Food and Drug Administration
Center for Biologics Evaluation and Research

26th Meeting of

The Allergenic Products Advisory Committee

December 11, 2013

FDA White Oak Campus
Building 31 Great Room A
10903 New Hampshire Ave.
Silver Spring, MD

PROCEEDINGS

Agenda Item: Call to Order and Opening Remarks

DR. NELSON: Good morning everyone. Don't mind the individuals running around fixing the audiovisual. They are going to work on this corner, which seems to be the only one out. Good morning again. Welcome to the 26th Meeting of the Allergenic Products Advisory Committee. I am Dr. Mike Nelson. I am honored to serve as your chair for today and tomorrow. At this time, I would like to call the meeting to order. We will begin by asking our designated federal officer, Mr. Don Jehn, to make a few announcements.

Agenda Item: Conflict of Interest Statement

MR. JEHN: Thanks Dr. Nelson. I would like to welcome everybody to today's meeting. Today's session is open to the public for the entire meeting. This meeting is described in the Federal Register notice of November 4, 2013. I would like to request that everybody check their cell phones to make sure they are on mute or vibrate.

Now, I would like to read in the public record the conflict of interest statement for today's meeting. The Food and Drug Administration, FDA, is convening the December 11 and 12, 2013 Meeting of the Allergenic Products Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972. With the exception

of the industry representative, all participants of the committee are special government employees, SGEs, or regular federal employees from other agencies and are subject to the Federal Conflict of Interest laws and regulations.

The following information on the status of this Advisory Committee's compliance with Federal Ethics and Conflict of Interest laws including, but not limited to 18 US codes Section 208 are being provided to participants at this meeting and to the public.

FDA has determined that all members of this Advisory Committee are in compliance with the Federal Ethics and Conflict of Interest law under 18 US code Section 208. Congress has authorized FDA to grant waivers to special government employees and regular government employees who have financial conflicts when it is determined that the agency's need for a particular individual service outweighs his or her potential financial conflict of interest.

Related to the discussion of this meeting, members and consultants of this committee have been screened for potential financial conflict of interest of their own, as well as those imputed to them including those of their spouse or minor children, and for the purposes of 18 US Code Section 208, their employers. These interests

may include investments, consulting, expert witness testimony, contracts and grants, CRADAS, teaching, speaking, writing, patents and royalties and also primary employment.

At today's meeting for topic one, the committee will discuss and make recommendations on the safety and efficacy of ORALAIR, a Sweet Vernal grass, Perennial grass, Timothy grass, Orchard grass, and Kentucky Bluegrass mixed pollens allergen extract, tablet for sublingual use, manufactured by Stallergenes. This is a particular matter involving specific parties.

For topic two, the committee will discuss and make recommendations on the safety and efficacy of grass tech, a Timothy grass pollen allergen extract tablet for sublingual use, manufactured by Merck. This is a particular matter involving specific parties.

Based on the agenda and all financial interest reported by members and consultants, no waivers were issued under 18 US Code 208. Dr. Robert Esch is serving as the industry representative acting on behalf of all related industry. He is employed by Greer Labs Inc. Industry representatives are not special government employees and do not vote.

There may be regulated industry speakers and other outside organization speakers making presentations.

These speakers may have financial interest associated with their employer and with other regulated firms. The FDA asks in the interest of fairness that they address any current or previous financial involvement with any firm whose product they may wish to comment. These individuals were not screened by FDA for conflicts of interest. This conflict of interest statement will be available for review at the registration table.

We would like to remind members, consultants and participants that if the discussions involve many other products or firms, not already on the agenda for which FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships that you may have with any of the affected firms, their products, and if known, their direct competitors. Thank you.

Dr. Nelson, turn it over to you.

DR. NELSON: Thank you, Mr. Jehn. Let me begin by thanking our many panel members today for their voluntary participation, their expertise, their time, and their preparatory work in advance of today's meeting. I would also like to thank them for their patience during travel to the DC area for this non-catastrophic, but very

disruptive weather we have had the last couple of days.

I thought I would begin by asking each of the panel members to introduce themselves. I will begin over here to my left with Dr. Esch.

DR. ESCH: I am Bob Esch and I am the industry rep.

DR. LIERL: I am Michelle Lierl from Cincinnati Children's Hospital.

DR. PETERSON: Jane Peterson, a retired public health nurse and anthropologist.

DR. SAPER: Vivian Saper from Stanford University.

DR. WEBER: Dick Weber from National Jewish Health in Denver.

DR. CASTELLS: Mariana Castells from the Brigham and Women's in Boston.

DR. RIEDL: Marc Riedl from the University of California, San Diego.

DR. NELSON: I am Mike Nelson, your chair, and also director for education training and research at Walter Reed National Military Medical Center and Office of the Surgeon General advisor for Allergy and Immunology.

MR. JEHN: Don Jehn, designated federal officer.

DR. KELSO: I am John Kelso from Scripps Clinic in San Diego.

DR. DAVIS: I am Carla Davis from Baylor College of Medicine, Houston, Texas.

DR. APTER: Andrea Apter from the University of Pennsylvania.

DR. RABIN: Ron Rabin from the Laboratory of Immunobiochemistry, FDA.

DR. SLATER: Jay Slater from the Office of Vaccines, Division of Bacterial, Parasitic and Allergenic Products.

DR. KRAUSE: Phil Krause. I am the deputy director of the Office of Vaccines Research and Review.

DR. NELSON: Thank you all again for making today's meeting possible. Before we begin today's exciting agenda and before I forget, let me thank on behalf of the entire panel the FDA and its leadership for being such kind hosts for us today particularly Mr. Jehn, Ms. Lipkind, and Dr. Slater for your preparatory work and hosting us in such fine fashion.

It is hard not to wax nostalgic entering into this 26th APAC meeting with so many historic firsts. This is the first meeting of this committee on this new FDA campus. It is the first new products in decades that have been brought before this committee. Its consideration of two new products on consecutive days and three in six weeks I think is also a historic first for this committee. And

then finally, it is the first ever consideration of sublingual products. We are very excited about what our sponsors are bringing before us over the next couple of days.

The importance of the topics to be discussed during these two days cannot be understated. Allergic rhinoconjunctivitis affects more than 50 to 60 million Americans and recently demonstrated to result in a loss of more than 3 million work days and 2 million school days despite the availability of subcutaneous immunotherapy and very high-quality medications.

Also, having read the sponsors' submissions, the rigorous science required and provided is at an all time high and all are to be congratulated for getting us to this point.

These submissions have the potential to refill the gap of home therapy with a potentially diseased modifying therapy created with the recommendation to cease subcutaneous home therapy due to safety concerns.

In order to efficiently and fairly address the ambitious agenda before us, I have a few announcements for the panel. All panel members are reminded to confine all of their discussions to these panel sessions itself and not discuss the information outside of the meeting session. We will conduct the agenda as listed and we are already a few

minutes behind so we will adjust it on the fly as needed. And although breaks are scheduled, feel free to get up and do what you need to do in the way of getting out to have yourself some refreshments or use the facilities right down the hall.

I will advise all the committee members to review the four questions that are in your packet. After today's presentations, we will discuss each of these questions in order including a vote later this afternoon. I believe they will also be introduced during Dr. Slater's presentation this morning. You will get a chance to see what is before you.

Welcome you all. It is going to be an exciting couple of days. I would like to now introduce Dr. Philip Krause, deputy director for the Office of Vaccines Research and Review at the Center for Biologics to recognize retiring committee members.

Agenda Item: Recognition of Departing Committee Members

(Presenting award. Mic at podium does not work)

MR. JEHN: Thanks Dr. Krause. I guess we are going to move on then to the first topic. Dr. Nelson.

DR. NELSON: Thank you. Our first topic today will be safety and efficacy of ORALAIR, a Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Bluegrass

mixed pollens allergen extract, tablet for sublingual use, manufactured by Stallergenes. Our first speaker to introduce today's topic is Dr. Jay Slater, director of Division of Bacterial, Parasitic and Allergenic Products, Office of Vaccine Research and Review of the FDA.

Topic 1: Safety and Efficacy of ORALAIR, a Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Bluegrass Mixed Pollens Allergen Extract, Tablet for Sublingual Use, Manufactured by Stallergenes

Agenda Item: Introduction, Background and Presentation of Questions

DR. SLATER: As you all know, this meeting was originally scheduled for the first week in November. That meeting needed to be cancelled. The ability to reschedule a two-day meeting on such short notice for so many people I think is a testimony not only to Mr. Jehn's determination to get this meeting rescheduled quickly, but to all of your commitment to the work that we are doing here today.

My job is actually fairly straightforward and it is to introduce you to the background on this presentation. I am going to be presenting an introduction and some background. Then you will be hearing a presentation from Stallergenes and then after a short break you will be hearing another presentation from Dr. Ron Rabin about the specific application.

My job is to introduce allergic rhinitis and allergic conjunctivitis to talk briefly about allergen immunotherapy, to talk some about what our considerations are in terms of efficacy studies for allergen immunotherapy focusing on clinically meaningful effects and certain challenges that we face with natural exposure or field studies. And finally, a few words about adverse events and special concerns on this class of medications.

As you have heard already, allergic diseases are important. They affect over 20 percent of the US population. It is a major cause of chronic disease in both adults and children. It includes allergic rhinitis, allergic conjunctivitis, which is our main consideration today, but also drug, latex, hymenoptera, and food allergy, anaphylaxis of all causes, and a subset of individuals who have asthma and eczema.

The management of allergic diseases is something that all of you are familiar with. It usually starts best with the identification of the offending allergen either by skin tests or by blood testing, instructing the patient on good avoidance measures, and frequently avoidance measures if possible can lead to a resolution of the allergic symptoms, but often that is not the case and pharmacotherapy is necessary. You are all aware that over the past 30 years there has been an explosion of novel

drugs for the treatment of allergy including H1 antagonist both oral and topical: topical corticosteroids, topical anticholinergics, mast cell stabilizers, leukotriene antagonists, and even some topical nonsteroidal approaches.

These medications are so good, so readily available that frequently both patients and their health care providers skip identification and avoidance and go straight to those. But in many cases, these approaches are not sufficient. An alternative approach that can work quite well is allergen immunotherapy in certain circumstances.

Which patients with allergic rhinitis and allergic conjunctivitis should be offered allergen immunotherapy? There is no uniform approach to this. The approach laid out here is described in the third update of the practice parameters for allergen immunotherapy that was published two years ago.

I think almost everybody agrees that in order for allergen immunotherapy to be effective, there must be clinical and immunologic evidence either based on skin testing or serum specific IgE of allergen interacting with the allergen-specific IgE as the cause. As an example, if an individual is skin test positive for short ragweed pollen, but the symptoms that they are having are not consistent with ragweed pollen induced rhino

conjunctivitis, it is extremely unlikely that they are going to benefit from ragweed pollen specific therapy and it should not be started.

In addition, as laid out in the practice parameters, health care providers and patients need to consider the clinical severity of their symptoms both in duration and effect on quality of life. The responses that they have had to avoidance measures and to pharmacotherapy including possible side effects, comorbid conditions that might complicate either pharmacotherapy or allergen immunotherapy and also convenience issues and costs of course.

Allergen extracts are a diverse group of products. They are both standardized and nonstandardized. They are of documented efficacy for both the diagnosis and treatment of allergic disease. They can be made from aqueous extraction of pollens, molds, epidermoids, insects, and foods. It should be noted that the foods are only approved for diagnosis, not for the treatment of allergic disease.

Let's talk for a few minutes about immunotherapy. The most common immunotherapy that is used is subcutaneous immunotherapy. It goes by several synonyms. They all have subtle differences in meaning, but they are often used interchangeably: desensitization, hyposensitization, most

commonly, allergy shots.

The approach involves the administration of increasing doses of allergen by subcutaneous injection. Conventional therapy. The doses are increased over a period of weeks to months. There are rush protocols in which this can be achieved in days to weeks. The rush protocols are associated with a significant increase in the incidence of adverse events.

Whether you use a conventional approach or a rush approach, the efficacy is clearly dose related. In other words, that maintenance dose that you reach is what is determinant of efficacy. And adverse events, which are all IgE-mediated, can be local, systemic, and fatal. The fatal events are extremely rare. Systemic events occur occasionally and local events are quite common.

Sublingual immunotherapy over the last decade or two has been increasingly used. It is an at-home regimen. There are various regimens that have been proposed in the allergy literature, mostly daily dosing, some of them five out of seven days, some alternate days. It has been increasingly used especially in Europe where there are two approved products for sublingual immunotherapy, ORALAIR, which you will be hearing about today, and grass tech, which you will be hearing about tomorrow under the name Grazax.

It is important to know that sublingual immunotherapy is used more widely that will be indicated by these two fully registered medications because of the extensive use in the EU of so-called named-patient products. Without going into it in great detail, these occupy a space between fully licensed products and investigational products. But they are widely available and widely used in Europe.

Finally, we do not have any specific numbers on this, but there is off-label use of subcutaneous immunotherapy products in the United States for sublingual administration.

Now, what I would like to talk about a little bit is how we evaluate these kinds of studies and what our expectations are in terms of the efficacy of allergen immunotherapy. Our current expectations are that clinical trials be double-blind placebo controlled field trials. This is our first preference for most of these kinds of trials and it remains that. But we have introduced the idea to this committee in our meeting in May 2011 of the possible use of direct challenge procedures. I will be talking somewhat about that in the next few slides as well.

In field trials, because it is very difficult if not impossible to recruit study subjects, if you do not allow them to use medications and the medications can

affect the symptom scores, it is important to use a combined score that incorporates both the patient symptoms and the medications that they need to use in order to get through the season.

And finally, we have some considerations about what we mean by a clinically meaningful response. I will be talking about that in the next several slides. What do we mean by clinically meaningful response? I think one thing we can agree on is that we do not mean simply a statistically significant response. We want to have a response that incorporates both symptom and medication use. If you look in the literature for suggestions as to the kinds of levels of a response would be considered clinically significant, it is actually hard to find that, but you see numbers of about 20 to 30 percent. The World Allergy Organization suggests that at a minimum a 20 percent response.

But what is important to note and we will dwell on this over the next several slides is that almost all of these proposals focus on the mean or average responses as 20 percent. And even though calculation of confidence limits has been encouraged in proposals in the past, in general, these confidence limits themselves have not been incorporated into pre-specified success criteria for allergenic studies.

The next series of slides are adapted from slides that this committee actually saw in May 2011. This was a presentation by Dr. Tammy Massie to introduce some of the concepts that we are going to talk about again today. And what you can see here are combined scores along -- I am going to describe it to you. If you look at the Y-axis of this graph, you see combined medication and symptom scores for a simulated allergy trial that follows two groups of study subjects through an allergy season. That season is 11 weeks long and we begin at the beginning of that season.

The two groups -- one group that is in blue is the group that received a placebo treatment and the group that is in red received the active treatment. And what you can see is that at the start of the allergy season at week 0, there is a substantial overlap between the combined scores of the two groups. That overlap decreases as you march through this 11-week season such that by the end of the season and actually from about six weeks on, you can see that there is very little overlap between the groups. And there is clearly open space between the scores of the two groups with the treatment group staying roughly down in the range below a score of seven or eight, and the placebo group creeping up to a symptom score, a combined score that is considerably higher.

The next slide shows exactly the same data, but

superimposed on that is the pollen count of this simulated season. This is what is behind this separation between the treatment and the placebo groups and that is the increase in pollen counts associated with the onset and continuation through the season.

This highlights two important points that we will come back to several times and that is that the performance, the apparent performance of an intervention in a clinical trial depends on things that we cannot control and that is the pollen count.

It also highlights the importance in this particular trial of identifying the beginning of that pollen season with some accuracy so that you can actually project patients onto this description accurately for analysis as well.

How do we actually analyze these data? Clearly, we cannot just look at these individual combined scores at each of the 11 weeks. Continuing with this simulation, we have now the mean and 95 percent confidence intervals of each of the sets of scores at each week for each of the two groups. The small crosshatch horizontal line represents the mean and the vertical line again either in blue or red represents the 95 percent confidence interval.

Now, one obvious way to look at the data is to just look at the differences of the mean values of the two

groups. At week 0, there is almost no difference in the mean value. Remember that is the time point at which there was a substantial overlap between the two groups set of scores. By week three, you can see that there is what appears to be a meaningful difference in the mean values between the two groups and that widens further in the calculated examples here at week 7 and week 10.

But what is important to look at is what the 95 percent confidence interval data are showing you. Let's look specifically at week 3 where the bracket shows a big difference between the mean values and yet the 95 percent upper limit of the treatment group and the 95 percent lower limit of the placebo group are almost touching.

Since the 95 percent confidence intervals tell us where that mean value will fall 95 percent of the time, there is a substantial likelihood that if we repeated this trial, we would see much less of an effect at three weeks because those 95 percent upper and lower limits are so close to each other.

Before we get much further into this -- by the way, this is the last time we are going to see the data analyzed in this way where we have both groups shown. As we go forward, the way the data are represented most of the time is looking at what these differences are. We will look at the differences in the mean scores and the 95

percent confidence interval of the difference in the mean scores.

But first of all, some conventional statements. By convention, we tend to look at score of treatment group minus score of placebo group. Therefore, with improvement, we expect to see a decrease in combined scores, a negative difference. We are not used to looking as bigger negative numbers as a good thing, but in this case, that is exactly what it is. And therefore, the 95 percent confidence interval upper limit of the negative difference is the least improvement that we can expect to see in the treatment group. We are going to be using this terminology fairly frequently.

Another comment since we are looking at negative changes, O negative differences between the groups, it is really important to listen to what your fourth grade English teacher told you and not use double negatives. Double negatives will make sentences almost incomprehensible in this group. A shout out to our English teachers. Let's listen to them. We will try not to use double negatives and hopefully we will minimize the confusion.

Remember I said that we were going to look no longer at the two separate groups, but rather an analysis of what those differences and mean scores are. This is one

way to look at that. Now what I have done is confusingly I have switched from vertical lines to horizontal lines. I apologize. In each of these situations, what we are looking at is the difference of mean score treatment minus placebo. That is why the zero point is on the right side and we are working in negative space. What you see along the X-axis is the zero point and a point called minus delta. That is what we are going to call for the moment the clinically meaningful margin, the point at which we have decided there is a clinically meaningful difference between the treatment and the placebo groups.

In the top horizontal line, the blue one off to the right, you can see that the mean value itself is very close to zero and the 95 percent confidence limits go almost equally to the left and right of the zero point. I think we can agree that this is a situation, which there is essentially no difference between the treatment and the placebo groups.

If you go down to the next line, you can see that the mean value is on the negative side of this minus delta, this clinically meaningful margin. And therefore, if you were looking only at mean values, this would look like a clinically meaningful change. However, the 95 percent upper limit of that study goes well inside the minus delta margin. And therefore, what we can predict is that if we

ran this trial a number of times, the data would look different and would span onto the other side of that clinically meaningful margin. This is a study that would be statistically significant. Look at that 95 percent upper limit. It is nowhere near zero. That would be a statistically significant study. But that would be a study that we would be concerned about that has not met our standard for being clinically meaningful.

The bottom line is one in which both the mean value and the 95 percent upper limit exclude this minus delta and therefore that is a clinically meaningful study.

This begs the question of course of how large the delta should be. We have agreed that an upper bound of the 95 percent confidence interval that excludes a pre-specified threshold of delta ensures reproducible statistical significance that translates into a clinically meaningful difference. How large should the delta be? That is not an answer that our statisticians can answer for us. Our current expectation is that a delta of minus 10 percent provides a reasonable assurance that the clinical effect that we are seeing is meaningful. Suffice it to say, however, that we need to consider the totality of the evidence regarding efficacy in order to make decisions.

I would like to talk a little bit more about natural field trials and some of the problems that we have,

some of the challenges that are associated with natural field trials. This has been discussed at great length in many different forums including in our May 2011 advisory committee meeting. This comes from a slide prepared by Dr. Rabin for that meeting. Because of the subjective nature of symptom scores and the high variance associated with symptom scores and the presence of poly-allergic individuals and on the other side our requirement for clinically meaningful differences between study groups. Pivotal trials for allergenics to prove efficacy of immunotherapy require multiple study sites, often in different geographical regions.

However, to induce symptoms as we discussed, pollen levels at each site must be high, sometimes for two or even three consecutive years. And therefore, studies of effective agents may fail due to low pollen seasons.

This comes from a study published in 2010 looking at annual grass pollen profiles in Washington, DC over a ten-year period. Without getting too deeply into this graph, you can see quite clearly that for each year, not only is the amplitude of the pollen season dramatically different going from as high as 80 to as low as 20 at the highest point. But you can also see that the peak season varies dramatically from year to year for a season that lasts only about six or seven weeks. And this study the

peak study varied as much as four to five weeks.

Pollen counts are highly variable within a single region. The challenge of pollen variability increases with the number of study sites. And variability in pollen seasons increases the variability of clinical symptoms enhancing the possibility of failure due to detect efficacy.

One possible solution to this challenge is the use of environmental exposure units, again, a concept that we introduced to this committee in May 2011. These are contained rooms in which exposure to airborne substances can be controlled. The studies are not limited to the period of natural pollination. It is controlled and uniform allergen exposure. There is no impact of weather conditions. There is no impact of lifestyle. It does not matter if your patients like to participate in outdoor activities or not.

You can assess responses to defined allergens even in poly-allergic individuals. You can ensure compliance. You can do timed symptom assessments. These kinds of studies allow you to use symptom scores only for the short period of time involved in the challenge. You do not have to offer people the opportunity to take their medications. However, these studies may not reflect real world efficacy. And therefore, we are reluctant to say

that we can approve certain products on the basis of a controlled exposure only, but that this could be a supplement.

This is again adapted from a slide from May 2011. Our approach to the controlled challenges versus the natural exposure really varies by the type of allergen that is being studied. I think we can agree that in the case of food allergen immunotherapy studies, controlled challenges are really the best approach both in terms of the efficiency of the study, its ability to make accurate biological predictions and the ethics of the studies as well. That is the case for high hymenoptera studies as well, in which really the classic studies were done by direct challenge and natural exposure studies probably have little if any place.

In terms of allergen immunotherapy for pet or animal allergens, there is a good argument to be made for both control challenges and for natural exposure. As I said in general for pollens and molds, our default approach has been for the use of field studies. But we can see in certain circumstances that the field studies may have weaknesses that can be made up for with judicious use of direct challenge studies.

EEUs are an attractive tool for supporting efficacy of novel products for allergen immunotherapy. EEU

studies alone may not be sufficient for demonstrating the efficacy of immunotherapeutics. Natural exposure studies may continue to be required.

Finally, I know we are behind schedule, but I would like to spend a few minutes talking about adverse events associated with immunotherapy. Adverse events associated with subcutaneous immunotherapy, as we said. The most common are local reactions at the site of injection, almost always on the upper arm.

Systemic reactions do occur on the conventional schedule. They are considerably rarer, occurring about three for every thousand injections or less. There are a number of studies, but that is about the highest number that you will find. Fatalities of course are much rarer. On average, about three or four fatalities a year. That comes out to about one in two and a half million injections.

In general, adverse events of interest in immunotherapy studies include both local reactions and systemic reactions. Systemic reactions can occur in both studies. They include wheezing, upper airway edema, urticaria, colic, hypotension, dysrhythmia, and death.

Local reactions of erythema, swelling, and pruritus as I said are very common in both kinds of studies. But a key difference is that with subcutaneous

immunotherapy, the reactions are at the injection site whereas for sublingual immunotherapy, the local reactions are in the mouth, lip, tongue and upper airway.

These two images come from one of several recent studies looking at tomographic approaches to measuring the size of the airway. And they are merely here to highlight that the airway is not a very large space and it gets smaller. It is smaller in young children than it is in adults. The local reactions that we know are common with sublingual immunotherapy are mostly just irritating and annoying, but potentially there are serious consequences associated with oral sublingual administration, which has been a concern of ours in all of these studies and will be a concern of ours as we go forward with these products.

Finally, one other consideration that I wanted to point out to the committee is that there are several populations of patients that those of us who administer subcutaneous immunotherapy have been taught over the years to be careful of and to think twice about whether to start them on subcutaneous immunotherapy. Again, this comes from the third update of the practice parameters. It includes young children under five years of age, the elderly, pregnant women, individuals with poorly controlled asthma and other comorbid conditions, people with a history of anaphylaxis, and person s taking specified concurrent

medications that enhance the likelihood of a reaction or that might interfere with responses to rescue medication.

It is important to point out to the committee that in all of the studies that you will be hearing, these individuals were specifically excluded from study. We have information about the safety and efficacy of these products in an important population, but in these populations that we have all been taught to avoid or to think twice about for subcutaneous immunotherapy, we actually do not have that much safety information on these individuals with sublingual immunotherapy either. It is something to think about as we go forward with our discussions.

I would like to show you the questions that we are going to be asking the committee to discuss today. The first two questions are questions that involve yes/no votes, but we hope will also involve significant discussion before the yes/no votes. Do the available data support the efficacy of ORALAIR for the treatment of grass pollen-induced allergic rhinitis or conjunctivitis in persons five years of age or older, when administered prior to and during the grass pollen season? Please vote yes or no.

Question number two. Are the available data adequate to support the safety of ORALAIR when administered to persons five years of age or older? In your deliberations, please consider the available safety data

for children and adolescents, adults, and the elderly. Please vote yes or no.

Please discuss whether the available data support the continued efficacy of ORALAIR through A, one and B, two years following courses of treatment for the previous three grass pollen seasons.

And the fourth question. Please comment on what additional studies, if any, should be conducted post-licensure. Thank you very much.

DR. NELSON: Thank you, Dr. Slater. We will now move on to the presentation by our sponsors in Stallergenes. I believe Dr. Lang is going to lead.

Agenda Item: Stallergenes Presentation

DR. ZELDIN: Members of the Advisory Committee, FDA representatives, and members of the audience, good morning. My name is Robert Zeldin and I am the senior vice president of Global Clinical Development at Stallergenes. On behalf of my colleagues, I would like to thank you for the opportunity to discuss ORALAIR, a sublingual tablet for the treatment of grass pollen induced rhinoconjunctivitis.

ORALAIR contains an allergen extract made from pollens of the following five grasses: Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Bluegrass. These grasses are among the standardized grasses approved by the FDA for the skin test diagnosis and subcutaneous

treatment of allergy. ORALAIR's potency is measured using both IR and BAUs. IR or index of reactivity is an in-house potency unit. One hundred IR per mL is defined as the concentration that elicits a wheal size of seven millimeter in diameter by skin prick testing. The corresponding range of potency will also be provided in BAU, the unit used by CBER for standardized grass pollen extracts.

These five grasses are broadly distributed across the US where 24 to 44 percent of the population is sensitized to grass allergens. As you can see from this slide, the five grasses are present in 85 percent of the counties in the United States. Therefore, ORALAIR contains grass pollens to which most US patients are exposed.

ORALAIR received its first marketing approval in Germany in 2008. Today, it is approved in 29 countries including France, Spain, Italy, Australia, and Canada. The post-marketing experience includes more than 20 million doses and more than 112,000 patients including more than 37,000 children and adolescents. There have been no marketing authorization rejections, withdrawals, or suspensions due to safety concerns.

We are proposing the following indication for ORALAIR. ORALAIR is indicated for the treatment of grass pollen-induced allergic rhinitis or conjunctivitis confirmed by positive skin test or in vitro testing for

pollen-specific IgE antibodies for any of the five grass species included in this product. ORALAIR is approved for use in persons five years of age and older.

Our presentation today will include the following. Professor Wahn will start with an overview of allergic rhinoconjunctivitis, its burden, and the unmet medical need. Then I will describe the development program for ORALAIR and will review the main efficacy results. Dr. Brigitte Bons will describe the safety experience with ORALAIR and finally, Dr. David Golden will provide his clinical perspective on the benefit-risk profile of ORALAIR. In addition, we have Dr. Kushner and Professor Senn with us today to help address your questions.

And now I would like to invite Dr. Wahn to the podium.

Agenda Item: Scientific Background

DR. WAHN: Thank you, Robert. Good morning. I am Ulrich Wahn. I am a pediatrician and professor of pediatric pneumology and immunology at the University Hospital of Charite in Berlin, Germany. I was the principal investigator for the pediatric study of ORALAIR. Today, I am a paid consultant of the sponsor, but I have no financial interest in the outcome of this meeting.

I would like to share with you some background on allergic rhinoconjunctivitis and the unmet need in this

area. As you all know, allergic rhinoconjunctivitis is a chronic disorder of the upper airways induced by allergen exposure and results in IgE-mediated inflammation of the nose and the eyes. Its prevalence has been increasing worldwide over the last decades. Approximately 30 to 60 million Americans are affected with a prevalence ranging from 10 to 30 percent of adults and as many as 40 percent of children.

Allergic rhinoconjunctivitis is associated with a substantial economic and social burden. In a statistical brief from the Agency of Healthcare Research and Quality regarding the trend and expenditures for allergic rhinitis, the author reported a doubling in mean health care expenditures from $6 billion in 2000 to $11 billion in 2005. There is also a striking impact on productivity with a considerable number of lost work days and days missed from school.

As a pediatrician, I would briefly like to share with you our own data on seasonal allergic rhinoconjunctivitis in the pediatric population. The clinical manifestations, which we see, start very early in life. Our prospective birth cohort study in children born in 1990 shows the highest annual incidence of seasonal allergic rhinoconjunctivitis in the first decade of life. Today in Europe, one out of five adolescents is affected.

Those affected and this is often underestimated by us physicians report significant impairment in the quality of life and especially in the daily activities as a result of this disease.

Furthermore, we know that children already diagnosed with seasonal allergic rhinoconjunctivitis at the time they first enter school have a significant risk of developing asthma over the subsequent years. Pediatricians are referring to this as part of the atopic march. Importantly, much of allergic rhinoconjunctivitis is caused by grass pollen.

Current options for addressing grass pollen induced allergic rhinoconjunctivitis are limited and avoidance of outdoor triggers such as grass pollen is quite difficult for practical reasons.

Among symptomatic pharmacotherapies, antihistamines have a relatively rapid onset of action. But many patients remain symptomatic. Leukotriene modifiers have a modest efficacy. Intranasal corticosteroids are more effective, but their effect takes longer. However, all of these therapies provide only temporary relief.

Allergen-specific immunotherapy is a therapeutic option that offers greater efficacy and can provide post-treatment benefit. Subcutaneous immunotherapy is available

in the United States whereas a standardized comprehensively studied sublingual immunotherapy is only available outside the US.

Allergen-specific immunotherapy is a therapeutic option for those patients who have symptoms not controlled by environmental avoidance or pharmacotherapy for those intolerant of symptomatic treatments and for patients who wish to avoid prolonged pharmacotherapy.

Subcutaneous immunotherapy is effective in treating seasonal allergic rhinoconjunctivitis upon reaching the maintenance dose. Despite this, only about 5 percent of the US population with allergic rhinoconjunctivitis, allergic asthma or both receive this treatment. Its use is limited by the discomfort and inconvenience of frequent injections and safety concerns, especially systemic allergic reactions.

Sublingual immunotherapy is currently marketed across Europe and in other countries including Canada and Australia. It is estimated that over one billion doses of sublingual immunotherapy have been taken by patients since the year 2000. The most recent Cochran Review states that sublingual immunotherapy is a viable alternative to subcutaneous immunotherapy with little difference in overall efficacy. The convenience and favorable safety profile of sublingual immunotherapy contribute to the

substantial and growing interest in its use.

This slide illustrates the proposed mechanism of allergen-specific sublingual immunotherapy. Within 15 to 30 minutes, the allergen is captured and processed by oral antigen presenting cells or APCs including Langerhans Lag Cells, myeloid and dendritic cells and macrophages. Within 12 to 24 hours, the APC is loaded with allergen-derived peptides reach the cervical lymph nodes where they interact with naive CD4 positive T cells to include T helper type one cells and T regulatory cells with immune suppressive activity within two to five days. These CD4 positive T cells sequentially migrate into the blood and to the tissue resulting in long-term allergen-specific tolerance.

The ability of sublingual immunotherapy to elicit tolerance is believed to be related to the number of peptide carrying APCs that stimulate resting T cells in the oral lymphoid organs. The favorable safety profile of the sublingual root can be explained by the lack of or limited release of intact allergens into the bloodstream, which is unlikely to stimulate systemic pro-inflammatory immune responses.

In summary, patients with allergic rhinoconjunctivitis need a treatment alternative because pharmacotherapy for control of symptoms is ineffective in many patients. And many patients do not tolerate

symptomatic pharmacotherapy or want to decrease the use of such treatment.

Subcutaneous immunotherapy is effective, but its use is limited by the discomfort and inconvenience of frequent injections and safety concerns.

Since its approval in Europe, sublingual immunotherapy with a standardized grass pollen tablet has become an additional valuable treatment option particularly for my pediatric patients. Thank you for your attention.

Now, I would like to turn it over to Dr. Zeldin again.

Agenda Item: Clinical Development, Program Efficacy

DR. ZELDIN: Thank you, Professor Wahn. Now, I will review the clinical development for ORALAIR. First, I will describe the study designs and efficacy end points. Then I will present the primary efficacy analyses of our adult and pediatric trials conducted in Europe, a confirmatory allergen exposition chamber study, and two additional studies, a long-term study and the US study.

Next, I will present the results of pooled efficacy analysis in pre-defined subpopulations. Then, I will present the results of our natural field studies using a common end point. And finally, I will discuss the clinical relevance of the data including the impact of

treatment with ORALAIR on quality of life.

We initiated our clinical development program in 2004 and have conducted a total of eight randomized double-blind placebo-controlled trials. The first is VO33.04 was a safety and tolerability study. The primary end points used in the efficacy studies evolved over time based on emerging data and the scientific literature and recommendations of regulatory authorities. The FDA has provided a summary of the end points on page 7 of their briefing document.

When we started these four European studies, the guidelines recommended using a total score of rhinitis and conjunctivitis symptoms as the primary end point. We termed this the Rhinoconjunctivitis Total Symptom Score or RTSS. This end point does not take into account use of rescue medication.

Subsequent guidelines recommended the use of an end point, which reflects the treatment effect on both symptoms and the use of symptomatic medications. We termed this the Average Adjusted Symptom Score or AASS.

Our long-term study was ongoing when these guidelines were published. The portico for that study was amended in the second year to incorporate the AASS. We also used the AASS in study VO60.08, which looked at an alternate dosing regimen.

Finally, in our US study upon request of the FDA, the primary end point was the daily combined score, which equally weights the symptom score and rescue medication score. All together these studies enrolled more than 2500 participants and more than 1500 received active treatment. I will describe each of the outcome measures in more detail in a moment.

Our study design was consistent across the natural field studies. Patients were screened starting about seven months prior to the expected start of the grass pollen season. Eligible patients were randomized to receive either active treatment or placebo beginning four months prior to the expected start of the pollen season and they continued treatment during the pollen season. This will be referred to as the four month, pre-seasonal and co-seasonal regimen.

Efficacy was evaluated during the grass pollen period as indicated by the shaded green box. This period was defined based on the measured pollen count at each study site according to pre-specified criteria. Patients continued to be followed for two weeks after treatment was stopped at the end of the pollen season.

We initially evaluated doses of 100, 300, and 500 IR. Based on the results of our safety and tolerability study and our adult registration trial in Europe and with

the objective of selecting the minimum dose required to obtain maximum efficacy, we selected 300 IR for evaluation in subsequent trials.

We also assessed the efficacy of two different dosing regimens that started dosing either four months or two months prior to the expected start of the grass pollen season. However, the efficacy of the two-month regimen was not demonstrated consistently. Therefore, the four-month pre-seasonal and co-seasonal regimen has been approved outside of the US and is the regimen for which we are seeking approval in this country.

Finally, in our initial studies, including the pediatric study, we used a three-day dose escalation scheme. That is 100 IR on day one, 200 IR on day two, and 300 IR on day three. Then with increased experience with the 300 IR tablet, direct administration without up dosing was used in subsequent studies including the long-term and US studies.

Because we have not tested direct administration in a pediatric population and all of our post-marketing experience is with up-dosing a three-day dose escalation phase is proposed for adults, adolescents, and children.

Patients assess their rhinoconjunctivitis symptoms daily on a scale of zero to three as shown here with zero being the absence of symptoms and three being

severe symptoms. The Rhinoconjunctivitis Total Symptom Score or RTSS was the total of the six individual symptom scores resulting in a daily RTSS ranging from zero or asymptomatic to 18 meaning that all six symptoms were severe.

In addition, each day patients recorded their use of rescue medication. The daily Rescue Medication Score or RMS was defined by Stallergenes based on the rationale that a nasal corticosteroid is more effective than an antihistamine and an oral corticosteroid is more effective than a nasal corticosteroid leading to a derived ordinal scale ranging from zero, which equals no medication, to three, which equals oral corticosteroid. The daily combined score is a composite end point that puts equal weight on the daily rhinoconjunctivitis total symptom score and the daily rescue medication score. It is expressed on a scale from zero to three.

Patients recorded their symptom scores and medication use on daily record cards. Depending on the study, the primary efficacy end point was the average or the daily score during the pollen period. It was analyzed using a linear model and analysis of covariance to estimate the difference in least squares mean between active treatment and placebo.

For all analyses, the probability of a type I

error or alpha was set at 0.05. And all inferential tests were two-sided.

Our patient population included adults, adolescents, and children at least five years of age. All patients had to have a history of grass pollen-related allergic rhinoconjunctivitis for at least the two previous pollen seasons. They also had to have evidence of grass pollen-specific IgE antibodies based on prick skin testing with or without in vitro testing. In addition, patients had to have a retrospective rhinoconjunctivitis total symptom score of at least 12 based upon their recall of symptoms during the most severe days of the previous grass pollen season. Our study population was consistent with the FDA's recommendations in the draft guidance dated April of 2000.

Patients were excluded from the studies if they were suffering from allergic rhinoconjunctivitis due to allergens other than grass pollen during the grass pollen season or they had asthma requiring treatment with other than beta-2 agonists. Of note, patients with mild intermittent to asthma were permitted to participate. In addition, patients were excluded if they had been desensitized to grass pollen in the preceding five years or receiving ongoing immunotherapy with any other allergen. Or they were being treated with beta-blockers, continuous

systemic corticosteroids or immunosuppressive agents.

Turning to the results, let's begin with the primary efficacy analysis for each of the four natural field studies, which evaluated the four-month pre-seasonal and co-seasonal regimen as well as the results of the allergen exposure chamber study.

Study VO34.04, the adult registration trial in Europe, was conducted at 42 centers across ten European countries. It was designed to evaluate the efficacy and safety of three doses of ORALAIR, 100 IR, 300 IR and 500 IR compared with placebo. As I mentioned, this study and the pediatric study used a build up phase at the start as shown by the gray box. 628 participants, aged 18 to 45 years, were randomized to treatment starting four months before the expected onset of the grass pollen season. The primary efficacy end point was the average Rhinoconjunctivitis Total Symptom Score during the pollen period.

As can be seen here, the patient population study review of 34.04 was balanced between the treatment groups in terms of demographics and baseline characteristics. This is the population that was evaluated for efficacy. Age ranged from 18 to 45 years with a mean of approximately 30 years. Roughly, 10 percent of patients had intermittent asthma and slightly more than half were poly-sensitized. The average duration of rhinoconjunctivitis was 12 years

with some patients having suffered nearly all of their lives.

And finally, at screening, the retrospective Rhinoconjunctivitis Total Symptom Score based on the evaluation of the most severe days during the previous pollen season was approximately 14 in all age groups.

The study met its primary end point. It demonstrated statistically significant reductions in the average Rhinoconjunctivitis Total Symptom Score compared with placebo in both the 500 IR and 300 IR dose groups. These differences represent relative LS mean differences of minus 24.7 and minus 28.2 respectively compared with placebo. In contrast, the difference between the 100 IR group and the placebo group was not statistically significant.

The increase in grass pollen specific IgG4 in this study confirms the immunologic activity of ORALAIR and was replicated across the development program.

Study view 52.06 was our pediatric trial. It was conducted at 29 centers across five European countries. 278 participants, aged 5 to 17 years were randomized to ORALAIR 300 IR or placebo starting four months before the expected grass pollen season with dose escalation. As in our adult registration trial, the primary efficacy end point was the average Rhinoconjunctivitis Total Symptom

Score during the pollen period.

Again, one can appreciate that the treatment groups were well balanced. Age ranged from 5 to 17 years with a mean of approximately 11 years. Approximately 21 percent of patients had intermittent asthma and nearly 60 percent were poly-sensitized.

As with the adult study, the primary efficacy end point was met in this trial. Active treatment with the 300 IR dose resulted in a statistically significant reduction and the average Rhinoconjunctivitis Total Symptom Score compared with placebo. This difference represents a relative LS mean different of minus 25.5 percent, which is consistent with what we observed in the adult study.

Study view 56.07A was a confirmatory study that evaluated ORALAIR in the controlled conditions of an allergen-challenged chamber. This study was conducted in Vienna, Austria outside of the grass pollen season. 89 participants aged 18 to 50 years were randomized to receive ORALAIR 300 IR or placebo once daily for four months. The use of rescue medication was not permitted. Allergen challenges were conducted at baseline and on day 7, one month, two months, and four months after initiating treatment. The primary efficacy end point was the average Rhinoconjunctivitis Total Symptom Score during a four-hour allergen challenge performed after four months of

treatment.

As in the other studies in the program, the treatment groups and study VO56.07A were generally well balanced. The mean age was approximately 27 years. Fewer than 10 percent of patients had intermittent asthma. There was a slight imbalance between groups on this parameter likely due to the size of the study. Approximately 70 percent of patients were poly-sensitized.

The results of this study demonstrate the robustness of ORALAIR's treatment effect and provide confirmation in a controlled setting of the efficacy observed in trials conducted under natural field conditions.

Now, I would like to turn your attention to the long-term study, which was designed to evaluate sustained and post-treatment efficacy. Sustained clinical efficacy was defined as continued efficacy during the second and third pollen periods. This study was designed as a four-year study with three treatment years and one treatment free follow up year. At the end of year three at the recommendation of the Data Safety Monitoring Board, it was extended for an additional treatment-free year. Post-treatment efficacy was also evaluated during the fifth pollen period.

Patients were randomized to one of three

treatment groups: placebo or 300 IR starting four months that is on the slide 4M or two months or 2M on the slide prior to the expected start of the grass pollen season for three consecutive grass pollen seasons. The primary efficacy end point was the average adjusted symptom score during the third pollen period.

Demographics and based on characteristics show that the patient population in this study was similar to that in the European study and the treatment groups were well balanced. For the year three pollen period, which again was the primary end point, the difference in LS means of the average adjusted symptom score between the 300 IR four month and placebo groups was statistically significant. This represents a relative LS mean difference of minus 34.9 percent. Results over the first and second pollen period were also statistically significant in favor of the active treatment groups.

And next, I will present the results of study view of 61.08, the US study. The study was conducted at 51 centers and enrolled 473 participants aged 18 to 65 years. Patients were randomized to ORALAIR 300 IR or placebo starting four months prior to the expected start of the grass pollen season. At the request of FDA, the primary end point was the daily combined score, which equally weights the total symptom score and the rescue medication

score.

Treatment groups were well balanced. The mean age of patients in this trial was approximately 37 years. About 20 percent had intermittent asthma and nearly 80 percent were poly-sensitized.

Looking at the primary efficacy analysis, treatment with ORALAIR resulted in a significant improvement in the daily combined score during the pollen period compared with placebo. The relative LS mean difference compared to placebo was minus 28.2 percent, which is consistent with the results of the other natural field studies.

Lastly, I would like to share with you evidence from the long-term study suggesting that ORALAIR provides a post-treatment benefit. Shown here are the results of the daily combined score for each of the five pollen periods. As you can see, a post-treatment efficacy was observed in the treatment-free follow-up period with a relative mean difference compared to placebo of minus 25 percent and minus 28 percent in year four and year five respectively.

We also performed two pooled efficacy analyses of the daily combined score in those treated with 300 IR according to the four-month pre-seasonal and co-seasonal regimen.

The first analysis looked at the total population

and the second looked at the subset of adult patients 18 years of age and older. Each of these pooled efficacy analyses demonstrates statistically significant improvement in the daily combined score in the active group. These results, which reflect different levels of grass pollen exposure in different locations around the world, summarized the effectiveness of ORALAIR and provide a more precise estimate of the effect size. In addition, the efficacy results of the pediatric study were consistent with those of the pooled analysis in adults.

The efficacy of ORALAIR 300 IR was also consistent across pre-defined subpopulations. Specifically, for patients who were mono or poly-sensitized, those with or without asthma, children and adults, males and females, and across different levels of pollen exposure, we observed a consistent treatment effect with ORALAIR.

To complete the review of the efficacy data, I would like to share results across studies using a common end point and provide an assessment of the clinical relevance of the data. Shown here are the efficacy data across natural field studies based on the daily combined score. The differences between ORALAIR and placebo were statistically significant for each study and correspond to relative LS mean differences ranging from minus 28 to minus

38 percent. These data support the consistency between the European and US studies and between adult and pediatric populations. In addition, similar analyses show that the efficacy results were consistent and statistically significant across studies based on the daily Rhinoconjunctivitis Total Symptom Score and rescue medication score indicating that neither the total symptom score nor the rescue medication score contributed disproportionately to the results you see here.

Clinical relevance means that the treatment effect is large enough to be important to patients. While there is no consensus on what is considered a clinically relevant improvement in allergic rhinoconjunctivitis symptoms, Stallergenes has sought to contextualize the clinical relevance of treatment with ORALAIR.

Shown here are the relative LS mean differences compared with placebo based on the primary end point in each of the efficacy studies. In each study, the treatment effect exceeds the threshold recommended by the World Allergy Organization taskforce, which stated that the clinically relevant efficacy should be at least 20 percent higher than placebo.

In addition, as detailed in the briefing document, the effect of ORALAIR on symptom scores compares favorably to that of the pharmacotherapies indicated for

treatment of seasonal allergic rhinitis although comparison across these must be done cautiously. Also, the effect size observed in the clinical program for ORALAIR is consistent with that of subcutaneous immunotherapy as defined by Dr. Lin and colleagues in a recent review of the efficacy effectiveness and safety of allergen-specific immunotherapy conducted for the Agency for Healthcare Research and Quality.

We also assessed patient quality of life using Dr. Juniper's Rhinoconjunctivitis Quality of Life Questionnaire or RQLQ. This validated tool was designed to assess the change in quality of life in adults with rhinoconjunctivitis. Scores ranged from zero to six. The lower the score, the better the patient's quality of life.

In our adult natural field studies, the RQLQ was completed at the visit at the expected peak of the pollen season. The overall RQLQ results demonstrate that treatment with ORALAIR 300 IR favorably impacts a key patient-reported outcome measure with relative improvements of 20 to 30 percent for ORALAIR versus placebo.

It is really important to note that in each study, rescue medication scores were higher in the placebo group than in the active group. Therefore, the true impact of ORALAIR on patient's quality of life as measured by the RQLQ is consistently underestimated.

In summary, in each of the natural field studies, the efficacy of ORALAIR 300 IR was demonstrated. The results of the allergen exposition chamber study are confirmatory. Secondary efficacy end points including Rhinoconjunctivitis Total Symptom Score, rescue medication score, and results of the patient reported Rhinitis Quality of Life Questionnaire consistently favored ORALAIR. A post-treatment effect was observed in the long-term study. The pooled analysis showed a similar treatment effect in all subpopulations. The results achieved with ORALAIR compare favorably with other treatment options and exceed the threshold for clinical relevance established by the World Allergy Organization. Overall, the totality of the evidence supports the robustness of the treatment effect and its meaningfulness to patients.

And now, I would like to invite Dr. Bons to review the safety data.

Agenda Item: Clinical Safety and Pharmacovigilance

DR. BONS: Thank you. Good morning. My name is Brigitte Bons. I am vice president of Pharmacovigilance at Stallergenes. It is my pleasure to share with you key elements of our safety data for ORALAIR. We will review data across eight randomized clinical trials, two post-authorization safety studies, and five years of post-

marketing surveillance with over 112,000 treated patients. I will then present data on specific populations including patients with asthma and the pediatric population. I will end my presentation with a description of our proposed pharmacovigilance plan.

Across our clinical development program, patient exposure was similar between the active and placebo groups. The mean duration of treatment was 204 days in those receiving active therapy and 212 days in those receiving placebo. More than 500 patients received active therapy for 6 to 12 months and 180 patients for at least 12 months over two or three pollen seasons.

Treatment Emergent Adverse Events or TEAEs were defined as any adverse event that occurs from the first dose of therapy and up 30 days after their last administration. Overall, adverse events were reported at similar frequency in active and placebo-treated patients. Fifty-eight percent of patients in the active group and 20 percent in the placebo group reported adverse events that were considered to be drug related. They are mostly mild to moderate in severity and they were related to application site infections. I will show more details about these events with you in a few minutes.

Serious adverse events were reported in 1.5 percent of actively treated patients. Importantly, none of

these events reported anaphylaxis and no epinephrine was used in any patients receiving active treatment. Three of the serious adverse events in the active treatment group were deemed to be treatment related by the investigator and are further detailed on the next slide.

Each of these cases occurred in the method treated with 300 IR. Two of the three cases were application site reactions. The first case in a 30-year-old male with laryngeal edema. It occurred within five minutes after the first dose and the patient was treated with an IV corticosteroid.

The second case in a 25-year-old female with a severe local reaction associated with coughing and dyspnea. It also occurred five minutes after the first dose. Symptoms were treated with an oral corticosteroid, antihistamines, and salbutamol. Neither of these patients was hospitalized. And both events resulted without sequelae.

The third case was gastroenteritis in a 43-year-old female, which occurred after three months of treatment while on vacation abroad. The patient was hospitalized and treated with antibiotics. This case also resolved without sequelae.

Given the similar route of administration we anticipate that the most frequent adverse events would be

of oropharyngeal in nature. Indeed, this was the case. The graph on the left shows that the common adverse events that were reported more frequently in the active group, as shown in green. This included events such as oral pruritus, throat irritation, tongue pruritus, mouth edema, and ear pruritus. The graph on the right showed the common adverse events that were reported more frequently in the placebo group in gray. These were generally consistent with rhinoconjunctivitis and included events such as nasopharyngitis, headache, cough, and sneezing. Of note, the majority of adverse events were mild or moderate. Those considered severe were reported at a similar frequency in the active and placebo groups 10 and 11 percent respectively.

We have also looked at the time to onset of both frequent adverse events. As you can see, the majority of these events occurred within the first week of treatment initiation most of the first day.

As detailed in our briefing document, adverse events lead to discontinuation in 5.1 percent of patients who received active treatment and in 1.2 percent of patients receiving placebo. In the active group, discontinuations were mainly due to oral pruritus and pharyngeal edema consistent with application site reactions. Most discontinuations occurred within the first

four weeks after study initiation.

Now, I will present the post-marketing experience with ORALAIR. We have analyzed data from two observational post-authorization safety studies as well as adverse reactions spontaneously reported over the past five years. The two observational post-authorization safety studies were conducted in Germany in 2008 and 2009 as part of the European Union restoration process. The objective of these studies was to monitor safety and relativity(?) of ORALAIR under usual conditions of use in the local market. Both of these studies used a three-day dose escalation.

More than 1700 patients were treated over one pollen season in the two studies. These included approximately 800 adults and 900 children and adolescents. In each of these studies, about one-third of patients experienced adverse reactions. The most common were application site reactions. This led to discontinuation in 9 percent of patients.

There were nine serious adverse reactions considered related to ORALAIR. There were no reports of anaphylaxis, no severe laryngopharyngeal reactions. No patient receives epinephrine and no hospitalizations related to ORALAIR.

In these two post-authorization safety studies, the safety profile of ORALAIR was similar in adults,

adolescents, children, and consistent with safety data from the clinical development program.

Since 2008, ORALAIR has been resistant(?) in 29 countries and is available in 22 countries. Over 20 million tablets have been prescribed through June of this year. We have estimated a number of patients treated with ORALAIR by taking the total number of doses sold, divided by 180, which is the average length of a treatment period. Based on this calculation, the exposure of ORALAIR is estimated at approximately 112,000 patients including approximately 37,000 children and adolescents. In this figure, the rates of all spontaneous reports, which are shown in green, and serious cases shown in blue, are displayed for each 12-month period since launch of ORALAIR. As shown, the rates of spontaneous reports declined over the first three years and have been stable since then. The rates of serious spontaneous reports have been stable over the entire period.

As shown by the curve, since the initial product launch, the number of tablets prescribed has increased considerably over the past five years and has more than doubled in the last two years. This indicates that with increased exposure, no safety signal has emerged.

Now, I will discuss adverse events of special interest. In this table, we show the reporting rates to

anaphylactic reactions and severe laryngopharyngeal reactions for all patients, others, and pediatric patients. According to the CIOMS classification of serums, which is the Council for International Organizations of Medical Sciences, the reporting rates of these events are considered to be rare to very rare. Anaphylaxis was reported by .011 percent of patients and severe laryngopharyngeal reactions were reported by .013 percent. The rates were similar in others and in children and adolescents.

Of the 12 cases consistent with anaphylaxis, two were considered by the reporters as unlikely to be related to ORALAIR. Eight of the remaining ten patients experience symptoms within 30 minutes of the first dose of ORALAIR, which was 100 IR. Two patients received epinephrine. All patients recovered without sequelae. The narratives are provided in the briefing document.

Fourteen cases were considered consistent with severe laryngopharyngeal reactions. In one of these cases, epinephrine was administered. However, the reporter considered that this reaction unlikely to be related to ORALAIR. All patients recovered without sequelae. Ten recovered within 24 hours. Narratives of these cases are also provided in the briefing document.

Now, I would like to show data on specific

populations including patients with asthma and the pediatric population. In the clinical development program, asthma was reported as a treatment emergent adverse event at a similar incidence in active and placebo groups. In the randomized clinical trials, 425 patients had intermittent asthma at randomization. Overall, the safety profile in actively treated patients with asthma was similar to that of patients without asthma. There was no increase in adverse events in patients with asthma who received active treatment.

Our pediatric study included 278 patients of whom 139 were treated with ORALAIR. At inclusion, 21 percent had intermittent asthma and 59 percent were poly-sensitized. There were no serious adverse events related to treatment. The most common adverse events were all local reactions. As in the other studies, approximately 5 percent of patients discontinued treatment as the result of adverse events. There was no worsening of asthma related to treatment. The safety profile in children and adolescents is generally consistent with that observed in others.

In the Pediatric Post-Authorization Safety Study that I described earlier, 457 children between the ages of 5 and 11 years and 372 adolescents between the ages of 12 and 17 years were enrolled. At inclusion, 36 percent had

intermittent asthma. The most common adverse reactions reported were throat irritation, oral paresthesia, oral pruritus, and mouth edema. Nine percent of patients stopped treatment because of adverse reactions. Five serious adverse reactions possibly related to treatment were reported. There were no cases of anaphylaxis or no case of severe laryngopharyngeal reactions. None of the patients received epinephrine and none was hospitalized as a result of treatment with ORALAIR.

Analyses of data from post-marketing surveillance including more than 37,000 children and adolescents shows that the reporting rates of adverse reactions and serious adverse reactions were similar in the pediatric and other populations. This is also true for reporting rates of anaphylaxis and severe laryngopharyngeal reactions. Of note, there have no reports of sequelae as a result of any of these reactions.

In summary, we have considerable safety experience in the pediatric population, which supports our proposed indication for use of ORALAIR in patients five years of age and older.

Now, I will present our proposed pharmacovigilance plan. In addition to routine pharmacovigilance activities, our proposed plan includes specific monitoring of severe laryngopharyngeal reactions

and anaphylaxis. Instructions for health care providers and patients by means of the prescribing information and patient information leaflet. These materials will require an office waiting period of at least 30 minutes after intake of the first tablet. It will inform physician and patients of the risks of anaphylaxis and severe laryngopharyngeal reactions and will describe the signs and symptoms of these events. It will instruct patients to seek immediate medical assistance should these events occur and will provide clear direction that treatment should only be resumed at the instruction of a physician.

In summary, we conclude that ORALAIR is safe and well tolerated. The safety profile is well characterized based on the analyses of more than 1500 patients in the clinical development program, more than 1700 patients treated in post-authorization safety studies as well as post-marketing exposure of more than 112,000 patients in 22 countries. Most adverse reactions were local reactions such as oral pruritus, throat irritation, and mouth edema. The vast majority of local reactions were mild to moderate. Rare cases consistent with anaphylaxis were reported in the post-marketing setting, but did not result in any long-term sequelae.

The monitoring for these events through our proposed pharmacovigilance plan gives us reassurance that

the benefits of ORALAIR will remain favorable. Thank you for attention.

Now, I would like to invite Dr. David Golden to the podium to conclude our presentation.

Agenda Item: Summary and Conclusions

DR. GOLDEN: Thank you very much, Dr. Bons. Good morning to the committee and the audience. I am David Golden. I am a practicing allergist and I am the chief of the Allergy Division at Franklin Square Medical Center in Sinai Hospital in Baltimore. I am a contributing author to the Joint Task Force on Practice Parameters on anaphylaxis and on immunotherapy. I am a member of the independent safety review committee for the ORALAIR clinical development program.

I would like to disclose that I am a paid consultant for the sponsor, but I will have no financial or personal benefit from the outcome of this meeting.

In my practice, I see people all the time who are frustrated by the options available to control their allergies. They have tried different pills, nose sprays and eye drops with limited relief. Some of them have started subcutaneous immunotherapy only to give up when their responsibilities keep them from getting to the clinic regularly and therefore failing to achieve effective doses. They tell me there is a need for something different,

something more convenient and effective, some new approach for control of their seasonal allergies.

To further understand this unmet need and why I am so encouraged by the data of ORALAIR, I will summarize the current treatment options for allergic rhinoconjunctivitis, their shortcomings, and the benefit-risk profile of ORALAIR.

As we heard from Dr. Wahn this morning, grass pollen induced allergic rhinoconjunctivitis is a disease that affects a substantial portion of the American population, millions of Americans of all ages, and can reduce their quality of life and productivity.

Unfortunately, the treatment effect of currently available medications is modest and temporary. Not everyone responds well to these medications. Symptoms tend to recur quickly. They also have adverse effects. They can be quite bothersome. Many patients have severe and prolonged seasonal symptoms for months and need multiple medications through the season. They often want to avoid extended use of so many medications so they are seeking alternatives for treatment.

Currently, immunotherapy is the only alternative for patients who do not get enough relief, have unacceptable side effects or just do not want to take so many medications so much of the time. Immunotherapy has

been shown to reduce symptoms and the need for medications. And the benefit can persist after discontinuation of therapy.

However, the only form of immunotherapy currently available in the US is by subcutaneous injection. This is effective, but its use is limited by the inconvenience of regular doctor's visits, the discomfort of frequent injections and the risk of anaphylaxis, which can be life threatening and rarely even fatal.

Sublingual immunotherapy has been shown to be effective while also offering greater convenience and a favorable safety profile. Although sublingual immunotherapy is not approved in the US, it is worth noting that some clinicians do prescribe for sublingual use the aqueous allergen extracts approved for subcutaneous immunotherapy. This practice simply reflects the unmet need for a more patient friendly form of allergen immunotherapy.

That brings us to ORALAIR. ORALAIR is a standardized pharmaceutical grade product that has been rigorously tested for efficacy and safety. I find the efficacy of ORALAIR in adults, adolescents, and children compelling. ORALAIR is effective in reducing both symptoms and the need for rescue medications. It improves patient quality of life. The data also suggests that the benefit

of ORALAIR persists after discontinuation of treatment.

In addition, the safety profile of ORALAIR is well characterized and very reassuring. This is based on the results of the clinical development program and more than five years of post-marketing experience including 37,000 children.

As with any form of allergen immunotherapy, systemic reactions can occur. But with ORALAIR, they are rare. Stallergenes has proposed a comprehensive, pharmacovigilance program that will educate patients about the risks and what to do should such an event occur.

Overall, it is my opinion that ORALAIR provides an effective therapy with a good safety profile that is a much needed treatment option for our patients.

Thank you for your attention. I would like to turn the podium back to Dr. Zeldin.

DR. NELSON: Thank you, Dr. Golden. And thank you, our sponsor, providing very comprehensive and thorough presentation of the product, safety and efficacy data for consideration of the committee.

I would like to ask the committee members at present. We are now scheduled to enter into a question and answer period with the sponsor. At your option, we will either proceed with that or take a quick break, which is schedule to follow the question and answer period. Any

preference? The military guy says let's drive on.

We will now proceed into the question and answer period for our sponsor. The floor is now open to the committee members to ask any questions that they may have.

Agenda Item: Questions

DR. KELSO: I have a question about the exclusion criteria. It was mentioned that patients clearly needed to be grass pollen allergic to be in the study. But it was also said that an inclusion criteria was they could not be allergic to something else at the same time. It was not entirely clear to me if these were patients who -- did that mean that they are not allergic to any other pollen that is pollinating at the same time as the grass pollen? Does it also mean that that you excluded people who are allergic to perennial allergens such as dust mite and cat and dog?

DR. ZELDIN: That is exactly as what you -- was exactly the case. If they were allergic to a pollen present and pollinating during the same season then they could not have been enrolled in the trial. If they were, for example, cat allergic and they were exposed to cat or were expected to be exposed to cat, they could not enroll. By contrast, if they were grass pollen allergic and also allergic to ragweed, which at least here in the Northeast the seasons are separate then they were able to enroll and indeed did enroll in our program.

DR. KELSO: I guess I have a comment about that. That makes it a little difficult to interpret the effectiveness in patients who do not meet that description because that is where they are relatively rare. Most people are allergic to lots of different pollens and many of them also to perennial allergens. I understand narrowing it to that group to see the effect on the grass pollen part of the allergy, but it kind of limits our ability to answer the question about effectiveness in patients who would typically be sensitized to more things.

But that also brings up the question. In another slide, you showed a subset of the patients who were described as being multi-sensitized and saying that the effectiveness was the same in the multi-sensitized versus mono-sensitized patients. But I am wondering given what we have just discussed, who are these multi-sensitized patients?

DR. ZELDIN: A multi-sensitized patient, for example, is the latter patient that I was describing to you. It is a patient who is grass allergic and also is ragweed allergic or is grass allergic and is cat allergic, but does not anticipate regular exposure to cat. And of course, I think your comment is well taken. In trying to evaluate the efficacy of a grass product including those other patients with multiple allergies would really

confound the ability to discern a treatment effect. It is a very challenging aspect of clinical research in this field of course.

DR. APTER: Two quick questions. One, with the symptom scores, most of these patients were followed for four months prior to the grass season and then before the six weeks of the grass season, was the symptom score calculated on all the days in the trial the four months prior or just during the grass season. How was that done? And then I have another question related to that.

DR. ZELDIN: The data that we have presented are the data over the pollen period. Patients completed their diary cards. They rated their symptoms. They noted their use of rescue medication. And then we evaluated the data over the pollen period for each and every one of the studies and for each and every one of the patients.

DR. APTER: So not over the four months prior.

DR. ZELDIN: They were asked to report symptoms and risk communication scores overall a wider period of time because of course, you cannot specify exactly when did the pollen season start in Colorado in May of 2012. They collected data for a wider period of time and then we looked at our protocol specified definitions for the onset of the pollen period and we took that chunk of data for each patient at each center in each study and evaluated the

data accordingly. I think your question was did we collect data for a longer period pre-seasonally and post-seasonally perhaps. And the answer is yes to be able to ensure that we appropriately bracketed the pollen period.

DR. APTER: And so for the last part of that question. As the tree season overlaps with the grass season, did you exclude patients that were tree allergic?

DR. ZELDIN: Yes, we did. We excluded patients who were tree allergic who symptoms based on the history were consistent with tree pollen allergy and who had positive skin tests or serum specific IgE to treat. Yes, exactly.

DR. CASTELLS: Thank you very much. I would like to hear more about the rationale between the severe adverse effects and anaphylaxis and laryngopharyngeal edema. According to the guidelines and our definition of an anaphylaxis laryngopharngeal edema would actually come into that definition. I see a lot of resistance in the description of the cases for the use of epinephrine. I would like to hear more about that particularly in the cases that I read. One woman with three days post-adverse event with cough and brown sputum. She was a really candidate for epinephrine. I would like to hear more about what definitions and if there was a limitation in the use of epinephrine in those cases.

DR. ZELDIN: Thank you for that question. With respect to anaphylaxis, there were no reports of anaphylaxis in the clinical development program for ORALAIR.

DR. CASTELLS: But it does not mean that the participants knew about the definition.

DR. ZELDIN: Clearly. Exactly. That is exactly why -- and of course we engage with talented investigators and we know their training and that is why choose good docs to conduct our trials. But nevertheless just to be sure we engaged a group of three external experts to help us to define anaphylaxis in the context of sublingual immunotherapy and then review in a blinded manner the totality of our clinical safety database to determine if perhaps there was a case that was not reported as anaphylaxis, but could have matched the criteria for anaphylaxis.

And Dr. Golden who is here and just spoke with you was a member of that group. I would like to give David the opportunity to describe the methodology that was used and the outcome of that assessment.

DR. GOLDEN: Thank you, Dr. Castells. That is a great question and it is a very important and central issue to sublingual immunotherapy. Let me try to address your question directly. I am not sure if we want to go through

-- and you can of course ask and I will be very happy to discuss in detail what our safety review committee did and how we evaluated the potential for anaphylaxis in the clinical development program.

At the core of that -- actually, maybe I will start with two or three slides. It will help me to address your question. Let me go to the next slide please. What we did is -- this was central to us asking ourselves as a committee what are we looking for when we are evaluating the safety database. We started with the NIH/SAMHSA symposium criteria for diagnosing anaphylaxis. I am obviously not going to go through this slide. You can see if you can see the fine print that there are in parentheses here a range of symptoms and signs that are associated with anaphylaxis. We also reviewed published epidemiologic reports of the characteristics of anaphylaxis and we developed a list of search terms.

Now the point is central to your question is that we in defining anaphylaxis in the context of sublingual immunotherapy, we excluded mucosal signs and symptoms. In the next slide, we will see the search terms that we used to query the safety database and you will see no mucosal signs and symptoms.

Let me be careful to point out. We were by no means ignoring this. This is critical. We are very much

concerned about the potential for severe adverse events including anaphylaxis and airway or laryngopharyngeal events. And obviously either one could be severe and of great consequence.

But the point is that we are actually following developing convention in sublingual immunotherapy to report these events separately. Application site reactions, which would involve the upper airway, are reported separately. They may be severe. They could be as bad or worse potentially than an anaphylactic reaction. But there are our application sites. They were presented and discussed separately. I am happy to say that even if we combined them, we are still seeing a rate that is extremely low for even for anaphylaxis, which again did not occur. It was not reported in the clinical development program. Again, part of the question is the patients do not the definition, but the investigators do. There were no reported events.

That was actually part of the reason that our safety review committee was convened to review the depths of the database for adverse events. That is the part that I may reserve for now and be happy to present it at any of your request. But I think I have tried to address your question that we are taking very seriously the upper airway events, the application site reactions and reporting them and discussing them.

Although in any other situation, they would be part of our evaluation for anaphylaxis. They are treated separately in this context.

DR. CASTELLS: Was there any evidence that tryptase was elevated in any of the cases or tryptase was not addressing any of the cases? Tryptase would be mass cell protease that would be associated with the development of systemic reaction even it starts at the level of the throat that we have systemic symptoms.

DR. GOLDEN: That would have been of interest. No. Tryptase was not evaluated in those cases.

DR. NELSON: Is there a follow on question to this line of questioning from the group?

DR. SAPER: It is a bit of a comment that I do agree with Dr. Castells. If you redefine what anaphylaxis is to exclude the application site reactions that you really do underestimate what the risk is. I think that in prescribing physicians going forward, it implies that that does not have the associated risk that you have indicated you believe could be associated. I think that there is a potential to have a disservice by separating those two out. Can you comment on that?

DR. ZELDIN: I think the intention was to more precisely define these sorts of events that occurred. We certainly worked very hard with David and Phil Lieberman

and Anil Brokow(phonetic) from Germany to capture any and every case possibly reported and to adjudicate them properly. When it comes to severe laryngopharyngeal events, as Dr. Bons shared with you, we had two in our development program. Those were two severe drug-related treatment emergent events. I could show that slide if it would be helpful. But those were application site reactions. Both occurred within minutes of the first administration of the product. Here we have a case of laryngeal edema and a case of a local allergic reaction with cough and dyspnea. We want to very comprehensively share these data and make it clear. How old is the patient? When did these symptoms occur? How were they treated and over what time period did they resolve? We are in no way trying to do anything but share them very transparently. But we feel that it is important to distinguish between anaphylaxis and in Dr. Slater's presentation, an upper airway reaction or a local or application site reaction. They are different entities even though as David has said, they are both important.

DR. SAPER: Although clinically for the practice and clinicians, it does underplay the significance of an application site reaction. And also as practicing clinicians, we know that immunotherapy or food reaction or other anaphylaxis can actually start with exactly the same

symptoms in the airway and those are not application site reactions. There would be no way that you could differentiate between the two. I believe that it is more fair to put those all together and then comment that this is the site of application and that these cannot be separated out. In that sense, you are not going to underplay and minimize the potential risk. That is one.

Two, I do not understand going through many of these reactions why adrenalin was not given. When you make comments that no epi was given, I believe that that is an irrelevant comment. I think the idea should epinephrine have been given is the more relevant. And the fact that it was not given then again downplays and unfairly minimizes the severity of the reaction. I believe that has really no place even in being mentioned. I think the reaction speak for themselves. And if substandard care was given according to you our sensibilities clearly the comment on adrenaline does not make sense at least to me. Comments?

DR. GOLDEN: If I may. I will make it very brief because I would like to address directly your very fair clinical question. First of all, I should mention when I said that we are following an evolving convention, what I meant is that there is a position paper published in the Journal of Allergy and Clinical Immunology this year by an international group addressing exactly this issue of the

report of application site reactions and sublingual immunotherapy. That is the evolving convention that we are following for reporting purposes and a description.

As I mentioned, I am happy to say that even if you rightfully I will say choose to include these application site reactions if they rise to a level of severity as a potential sign of an anaphylactic reaction, the combined occurrence of the application site reactions through five years of surveillance together with the report of anaphylaxis during that time period. We were talking 0.0 and 1 percent plus 0.1 and 1 percent. If we were to report all of that as let's call it systemic allergic reactions, it would be 0.0 to 5 percent. In the context of the occurrence rates and the reporting of these events for sublingual immunotherapy, we are very comfortable with our description of the product as having a very low risk for systemic allergic reactions.

DR. RIEDL: I just wanted to add a comment and then have a follow up question to this discussion. I agree with my committee members that it is a fair point that these reactions are at a very low rate. I do think that you are under playing the potential clinical significance of this. Frankly, under any other circumstances of food or any other exposure, I think these would be classified as potentially systemic events even if you look at the

definition of anaphylaxis, the timing including upper airway involvement significant enough to potentially have respiratory compromise. I have the same concerns that were raised about how you are classifying these. Personally, I think the presentation under played that potential risk even if it is very rare.

I also have just quickly follow up questions. I find it a little bit puzzling that in slide CS88 under the reasons why patients discontinued their treatment, which was 5 percent in this particular data set, that things that are included are vomiting, chest discomfort, urticaria, dyspepsia, esophageal pain. These are things that again depending on the timing of those symptoms within exposure would very well suggest potentially systemic reactions. I do not know if you have any comments or additional information you can give on the timing of these sorts of symptoms that led to discontinuation of treatment in CS88.

Again, this may be too much to cover now. But I was curious about in the post-marketing reports there are at least ten cases of what were classified as anaphylaxis and at least 14 cases that were classified as severe laryngopharyngeal reactions. There was no mention of the treatment required for those particular reactions. I would be interested in that data as well.

DR. ZELDIN: For you first response, you asked

for a specific slide. I would like to share that with the committee. These are all adverse events leading to discontinuation at least 2 percent of patients in the active treatment group. As it states on the slide, 5.1 percent of patients discontinued, the largest number due to oral pruritus, pharyngeal edema, and upper abdominal pain as we go down. Events leading to discontinuation generally occurred within the first week or two of treatment initiation.

DR. RIEDL: Just as a follow up. Is there a reason why these were not considered to be systemic reactions?

DR. ZELDIN: These are in the clinical development program. Patients are all seen by the investigator, by the clinician at the site who makes the judgment as to how they are to be treated and in collaboration with the patient whether the patient should indeed discontinue. Of course, it is ultimately up to the patient. The terms as described are exactly what the clinician investigator submits to the company. Our objective here is again just to be completely comprehensive and to share with you the data as we receive them.

DR. KELSO: I think it is important going forward that if we ultimately approve this, that somehow it gets communicated. I think I am sensing a consensus on the

concern that they are not -- if I am the person who is just reading about this new product that is available, I do not want to be left with the impression that some people get an itchy mouth. Somehow, I need to know that that is different than somebody got an itchy mouth and somebody had airway compromised because that is not a local event or a topical event. Even if it is, it is more serious than just an itchy mouth. Again, the idea that because epinephrine was not used does not mean it should not have been used. Somehow, when we ultimately come to how this is presented to people who are going to be using this product, I think the potential seriousness of these events and the potential need for epinephrine needs to be emphasized.

DR. PETERSON: Changing the topic slightly, but I am all in favor for discussing epinephrine. The pre-season medication that you are given over four months before the pollen time, how is that calculated? My great concern since I worked with people on the ground is that they do not take it all the time. Nothing has happened today and I forgot it. It does not matter. Two days later, I should take it. Does that change the dosage or does that change your build up and the need for the medication? Do you have to start over again? How does that work?

DR. ZELDIN: Our recommended regimen is that patients start four months prior to the pollen season with

a three-day dose escalation phase. They reach that maintenance dose of 300 IR and they are to continue it through the end of the grass pollen season in their region.

Now, you asked a very important question regarding adherence or patient compliance. We have obviously collected compliance data in our development program. A compliant patient was defined as one who took at least 80 percent of the tablets that they were to have taken based on the length of the season. I am happy to share with you those data. In brief summary, the compliant patients were patients who were compliant who were in the 94 to 98 plus percent range in the development program. We had a very compliant population.

What is really interesting though is the data that Dr. Bons shared with you regarding our post-authorization safety studies. The studies are specifically designed to look at real life use of the product. And in both of those studies in one the adherence rates where patients' compliance was 93 percent and the other was 98 percent. We take that as very reassuring with respect to patient's engagement in taking this product.

DR. SAPER: As a follow on to that, how did you actually measure the adherence? Did you have some sort of a device that was date and time stamped for dispensing the medication or was this by patient questionnaire?

DR. ZELDIN: In the clinical development program, we counted tablets. In the post-authorization safety studies, it was by patient report in collaboration with the investigator.

DR. SAPER: I share Dr. Peterson's concern because people are people. If they are not going to have symptoms, there will be a percentage of people that are unlikely to take it. There are also people that feel they are supposed to be good and will tell you what you want to hear. Do you have any data that would let you know what happened if a patient was to begin treatment coincident with the onset of symptoms during the grass pollen season because that is when they are likely to remember to take their medications?

DR. ZELDIN: We have not specifically studied regimens other than the ones I have described to you. When clinicians treat patients with ORALAIR today in Europe, they are instructing their patients to begin therapy four months before the season and to continue it throughout.

DR. SAPER: You must have very compliant patients to have 94 percent do it exactly as directed or within 80 percent.

DR. LIERL: I have a few questions. First of all, it seems that there were a fair number of patients who discontinued participation due to early onset adverse

events. I think 5 percent in one study and 9 percent maybe in the pediatric study. Mostly the itchy mouth, throat swelling, that kind of thing. And then most of your severe adverse events also occurred within the first few days of treatment. It strikes me that this is a very different kind of regimen than subcutaneous allergen immunotherapy where we start with a very low dose and build it up more gradually just for that reason to avoid causing an allergic reaction with too high of a dose. Did you ever try a slower build up phase to see if maybe it would be better tolerated and you would have less drop out?

DR. ZELDIN: As you said, the percentage of patients who discontinued across the development program was about 5 percent. Most indeed discontinued early on in the treatment period. As you well noted, the very few severe adverse events, the two that were considered by the physicians to be serious drug related adverse events both occurred on the first day and within minutes of dosing. Application site reactions or local reactions are certainly common. We reported rates in the 60s or so percent and considerable numbers actually in the placebo group as well. But you asked a very specific question. Did we assess regimens other than 100 IR a day, 200 IR a day, or direct administration? And the answer is no.

But what we did observe when we compared patients

who received that three-day dose escalation phase is a near having of the rate -- the incidence of application site reactions in those patients compared to those who went to direct administration with 300 IR. It is for that reason that we are recommending here as has been approved in the rest of the world that a three-day dose escalation regimen or up dosing over three days be recommended for exactly the reason that you have articulated and of course the fact that the totality of our post-marketing experience as Dr. Bons shared with you of 112,000 patients treated is using that regimen. We think that that experience is valuable to incorporate in the totality of the understanding of the product.

DR. LIERL: Do you think it might be worth a trial of a slower escalation just to see if you can improve safety and tolerability?

DR. ZELDIN: It is an interesting question. We have not considered that today. That is an interesting question. Thank you.

DR. LIERL: And then I have another couple of questions. What did you tell your subjects to do -- a fair number of your subjects had well-controlled asthma on entry to the study. What if they had an asthma exacerbation? Did you tell them to hold the treatment?

DR. ZELDIN: Let's share the data on asthma. I

think it is very informative. Asthma as an adverse event was reported at a similar rate in those who received active treatment versus placebo. We asked the patients who were experiencing an exacerbation to contact their doctor and the doctor was to use their judgment. Our advice was to discontinue therapy and address the asthma. Patients with unstable asthma, uncontrolled asthma, asthma experiencing exacerbation should not be the type of patient who receives allergy immunotherapy. That was our guidance. To the best of our understanding, that is exactly what was followed.

What was interesting was that across the development program there were a total of 13 patients recording a need or received a corticosteroid burst because of asthma exacerbation. We thought it was striking. We are certainly not making any claim as to efficacy for the treatment of asthma. Three of those were actively treated patients, just 1.2 percent, compared to ten were 5.5 percent in placebo-treated patients. It is interesting to us. Frankly, we found it reassuring that this product does not result or prompt a worsening of asthma. To answer your question very directly, yes, our advice was and would continue to be that patients who are experiencing asthma exacerbation should not be administered immunotherapy of any nature, sublingual or other.

DR. LIERL: Just one more question. I did not

see eosinophilic esophagitis addressed as an exclusion criterion. There are in your list of adverse events occurring in two or more subjects on active treatment, there are several symptoms that sound like eosinophilic esophagitis symptoms like dysplasia, upper abdominal pain, and esophageal pain. Do you have any inkling of whether the sublingual immunotherapy could trigger symptoms of latent eosinophilic esophagitis?

DR. ZELDIN: Very interesting question. I think the best way I can answer it is to say that most of these events of the local or application site reactions result spontaneously without treatment and did not by far result in discontinuation of therapy. Most patients just played through. In the handful as you saw who discontinued, all of those events resolved spontaneously with -- resolved with discontinuation of therapy. We followed each patient carefully after their withdrawal and we followed them until resolution. That is a very important question. I think we can very definitely answer it.

DR. NELSON: Colleagues on the panel, I would like to thank you for your thought-provoking questions. I actually haven't gotten to half of the ones that I had on my own list. We will have the opportunity to continue to ask the sponsor questions during our discussion phase this afternoon. It is probably a good time for us to take a

break. We are about 15 minutes over for this session, but we will probably make up some time during the public hearing phase. We will reconvene in 15 minutes, which I have as 11:40.

(Break)

DR. NELSON: Welcome back ladies and gentlemen. We will now proceed with the remainder of our agenda for the morning. Next up is the FDA presentation on their review of ORALAIR. It will be presented by Dr. Ron Rabin, Chief of the Laboratory of Immunobiochemistry.

Agenda Item: FDA Presentation

DR. RABIN: Thank you, Dr. Nelson. What I will be doing is I will be reviewing really some of the basic efficacy and safety data that have concerned us most in review of this product. I think that you have all had a pretty comprehensive review of the data from the sponsor. It is not our intention to repeat all of those data for you. I will discuss briefly the product description, the proposed indication, the efficacy and the safety data and the post-marketing studies.

ORALAIR is a tablet manufactured from an allergen mixture that is obtained by concurrent extraction from five different grass pollens. All of those are in the same family and sub-family. And the five pollens are, as you have heard, Kentucky Bluegrass, Orchard, Perennial Rye,

Sweet Vernal, and Timothy.

It is a rapidly dissolving tablet for sublingual administration. The potency is defined and the index activity in 100 IR elicits a wheal size of seven millimeters in 30 sensitive subjects. That is how the sponsor defines its IR units. And the tablets come in the 100 IR for initial dose escalation and 300 IR for maintenance in children and adults.

As you have heard, the sponsors' proposed indication and usage are that ORALAIR is indicated for the treatment of grass pollen induced allergic rhinitis or conjunctivitis confirmed by positive skin test or in vitro testing for pollen-specific IgE antibodies for any of the five grass species included in this product. ORALAIR is for use in persons five years of age and older.

There were seven clinical trials, a phase I safety study, a phase II dose ranging study and then five phase III trials, as you have heard. One of them was performed here in the United States and the other four were performed essentially in the European Union.

The efficacy data just to review the key subject criteria for these phase III studies. They had to be grass pollen. They had to have grass pollen related allergic rhinoconjunctivitis for at least two previous seasons and score greater than 12 out of a possible 18 on the

retrospective symptom scoring for the previous grass pollen season.

The diagnosis of grass pollen. There had to be a diagnosis of grass pollen allergy. Positive skin prick test to Timothy grass. In two of the studies, the adult US study and the pediatric study and both positive skin prick tests in IgE for the other three studies.

The FEV1 had to be greater than 80 percent of the predicted value. The panel has discussed the exclusion criteria about subjects having a positive skin prick test to other grass allergens during this pollen season such as Bermuda, Bahia, and Johnson. Clinically significant allergy to perennial allergens as well and other allergens such as tree.

I want to point that the asthmatic subjects that were excluded from this study were those who required any medications other than intermittent beta 2 agonists. The general study design is that subjects were treated with ORALAIR placebo tablets sublingually each day. And as you heard in the pediatric study, there was a ramp up of three days. The treatment began approximately four months before the estimated start of the grass pollen season. At initiation of treatment, rescue medication and a daily record card were dispensed for the US study and EpiPen was also dispensed. Subjects returned two weeks later, three

weeks before the anticipated start of the grass pollen season in the middle of the season and at the end of the season. The treatment ended with the end of the grass pollen season and there was a last visit two weeks after the end of that season.

You have heard a bit about the scoring. I am just going to remind you of how the symptoms and medication use were scored. There is the rhinoconjunctivitis symptom score. One score for each of the allergic rhinoconjunctivitis symptoms, sneezing, rhinorrhea, nasal pruritus, nasal congestion, ocular pruritus and watery eyes. And there would be one score per day per subject. In other words, if you had a 100-day grass pollen season, there would be 100 scores from each subject. And then the rhinoconjunctivitis total symptom score would simply be the sum of those six symptoms. You notice that either of these or both of these can be averaged per subject over the pollen season to create the average RSS and ARTSS.

The rescue medication score was scored from zero to three, zero, no rescue medication taken. Three would mean an oral corticosteroid was taken. This RMS similarly can be averaged over a pollen season to create the AARMS.

Just to give you an example of the basic arithmetic, how might the difference in these combined scores be calculated? Imagine a placebo group with a

combined score of four, a study group with two. The difference would be minus two and therefore the percent difference in the combined scores would be minute 50 percent.

How do we assess the efficacy of the allergen immunotherapy? We have talked about what the important differences are. We considered the minimal clinically important difference, which is defined as the smallest change in the treatment outcome that a patient would identify that is important. The WAO was discussed. It drew this difference at a minus 20 percent and we looked at it from a standpoint of 15 percent improvement so a negative 15 percent change. But we also included as Dr. Slater discussed in great detail, the 95 percent confidence interval again, which is the range in which the point estimate would be included for 95 percent of the individual measurements. And the maximum value for this would be minus 10 percent.

Just to show you an example of two studies that would give the same difference, the percent difference in average scores. The top one in red and the bottom one in blue. But differences in this upper limit of the 95 percent confidence interval. One of them that is below this minus 10 percent threshold and we would regard as clinically meaningful. Therefore, we would regard the

results of that study as clinically meaningful. And the one in red in which the results are above that minus 10 percent level.

These are the phase III studies that the sponsor has presented to you. I think you have heard enough about them. Just to point out again that there was one study in the United States and the other four were performed outside of the United States. There was one pediatric study. There were two studies that assessed pre-treatment at two months prior to the grass pollen season and four that looked at four months prior to the season.

First to discuss the US study that we consider pivotal for safety and efficacy. It was performed in 2009 in 51 study sites in the US. This was the only study that the sponsor performed under IND. It was randomized one to one, placebo controlled, ages 18 to 65 inclusive, and treatment was initiated about four months prior to the grass pollen season. As the sponsor told you, the primary end point was the combined score.

Most of these result slides will follow the same format, which is to simply show you what this percent difference of average scores are for the primary end point or the combined score, which is on the right and then key secondary end points, the total symptom score and the medication score on the left. To start off on the right,

the difference -- it was minus 28.2 percent. The 95 percent confidence upper limit was less than minus 13 percent. And you will notice that that was the case for the medication score, but not for the symptom score, which again suggests that these subjects that took medication in order to relieve their symptoms and combining these scores together is a useful index by which we can measure efficacy.

The pivotal study for safety and efficacy in children was VO52.06. This was performed in 29 study sites in five European countries. Again, it was a one-to-one randomization placebo controlled study of children and adolescents aged 5 to 17. Treatment, again, was initiated four months prior to season. And the sponsor's primary end point parameter was the ARTSS.

But, again, for us, we were most interested in the combined score. And the percent difference in the average scores here was minus 30.1 percent. And the upper limit of the 95 percent confidence interval was minus 13.2 percent, which is below the minus 10 percent level that we are most interested. And then you can see here the symptom score on the left and the medication score in the center and the distribution of each.

The sponsors also performed the study VO60.08. This was a study that was supported for safety in adults.

It was performed in 2009 in 38 study sites in five European countries. Again, a one-to-one randomization. Subjects were aged 18 to 50 inclusive. For this study, the treatment was initiated two months prior to the anticipated start of grass pollen season. And the primary end point parameter here was the AASS, which is a sponsor derived symptom score that does take into account the medication score.

This study, as you can see, did not yield the clinical meaningful results. The percent difference of average scores was greater than minus 15 percent. It was 10 percent. Of course, the 95 percent confidence intervals were also not as I have defined earlier.

VO53.06 was the multi-year study that was performed from 2006 to 2011 in 45 sites in six European countries. Again, it was a five-year study in which years one to three were treatment years and then treatment was interrupted. There was no treatment from the end of one grass season until the time prior to the pre-treatment period before the anticipated start of the next grass season. And then years four and five were observation years or years in which there was no treatment. There was a randomization of one-to-one-to-one because treatment was initiated either two or four months prior to grass pollen season. You had two treatment groups there and then a

placebo group. The primary end point again was -- the sponsor's defined primary end point was the AASS for the third year.

These are the combined scores, again, the CS, for the first three years. The number of subjects that participated in each year in this two-month pre-treatment group for both the treatment and the placebo groups. The number of subjects in the third column. The fourth column from the left is the raw data that the number four, that combined score. And then percent difference in these scores as you can see is minus 20.7, minus 38.3, and minus 40.9 percent for those years of treatment in this two-month pre-treatment group.

Now, I have added to this table the two years in which there was no treatment, those observation years, years four and five. As you can see, the percent difference in the average scores was minus 31.1 and minus 28.2 percent for years four and five respectively. And the 95 percent confidence intervals, that upper limit, was minus 11.6 for the fourth year, but crossed zero and was plus 0.3 for the fifth year.

Now, these are the subjects who had the four month pre-treatment. The placebo numbers are the same. It was the same placebo group. The number of subjects in the ORALAIR group you could see what they were for each year:

188, 160, and 149 for years one through three.

The combined scores are shown in the fourth column and the percent difference of these combined scores as you can see for years one, two, and three were minus 16.4, minus 38.0, and minus 38.3.

Then adding the fourth and fifth no treatment or observation years for these same studies, you will notice that the percent difference in the average scores remained less than 15 percent. But that the 95 percent confidence intervals for these last years as it was for the first year in this group was greater than minus 10 percent.

For year one, the percent difference of the average scores whether or not they were less than minus 15 percent for year one in the four month pre-treatment -- that was true for all five years as you can see. But the 95 percent confidence interval whether or not is less than 10 percent that was only true for years two and three of treatment for this particular study, not for the first year and not for the two observation years in the four month pre-treatment group.

This is a summary of the combined scores from these four single year phase III trials. What we are showing you here are the mean data, which is the vertical bar for each of the double-headed arrows. And then the double-headed arrow, the length of that part itself is the

95 percent confidence interval for each of these. You could see that three of them did not cross the minus 10 percent level and two of them did.

Just to show you years. They are not labeled, but I think it would be intuitive to show you that years one through five for the two-month pre-treatment group on top in black and the four-month pre-treatment group on the bottom in blue and what those levels were and whether or not they crossed this 95 percent confidence limit, upper limit of minus 10 percent.

CBER then looked at additional efficacy data to support the phase III data. In that regard, we reviewed VO56.07, the study that was performed in the environmental exposure unit in Vienna, Austria. As the sponsor told you, these subjects were randomized one to one. Placebo controlled. Placebo re-treatment group and they were challenged in the environmental exposure unit for four hours prior to randomization. Outside of grass pollen season. Then they administered either placebo or ORALAIR. Kept diary record cards and then re-challenged in the EEU at various -- after on treatment week, one treatment month, and four treatment months. The primary end point was a symptom score, which of course is the only score that is really collected in this context because medications are not taken inside the chamber.

And to show you these data, again, as the sponsor showed you the end for the treatment and placebo groups was 45 and 44 respectively. And you can see the difference at baseline and after four months. If you look over in the far right column, you will see that the percent difference in the average scores was about minus 29 percent. The upper limit of the 95 percent confidence interval was indeed less than 10 percent as it was minus 13.7 percent.

Now, looking at the totality of these data, I have shown you again the first five rows of these data are the same as I showed you before. The combined scores. And then the bottom one in brown is the chamber study. We have considered these data as in their totality including the chamber study.

Moving onto safety. The safety monitoring as the sponsor has told you or the subjects were observed in the physician's office for 30 minutes after doses one, two, and three in the US. In the EU, it was only after day one. The subjects received a phone call on day four, which was the first day of at home administration. Subjects were submitted paper diary records, which included open-ended queries for adverse events. In other words, specific adverse events were not solicited. And the safety assessments of course were performed at study visits.

To define a treatment emergent adverse events, it

is any event that it started on or after the first administration of the investigational product. These adverse events were graded according to severity. You will notice that this is severity as graded by the investigated as reported by the subject. This gradation. It is important. It refers to discomfort of the symptoms. Mild, moderate, severe, or of course absent, which was left off here. Mild being easily tolerated. Moderate is causing discomfort, but were tolerated. But they could not be ignored. And then severe would mean that these symptoms affected usual daily activity.

This gradation is different than considering a serious adverse event, which is considered one that would jeopardize health in some way or a fatality, life threatening that causes a persistent or significant disability or capacity. Requires hospitalization or prolonged hospitalization or causes a congenital abnormality or defect.

The safety database includes the seven clinical trials for a total of 2512 subjects, 1514 of them who received the study drugs, and 998 who received placebo. The safety analysis was based on two analyses of the subjects that were randomized to receive the ORALAIR. Adults greater than 18 years of age or children or adolescents 5 to 17 years.

For adults, there were 1038 adults who received ORALAIR and 840 who received the placebo. Their mean ages were similar as were the percent who had asthma and the mean duration of exposure is 137 days.

The TEAE of adults. This is really only for that first year. The ones that were most common were these local symptoms of itching of the month and throat irritation. But there were a number of others that were reported at a frequency of greater than 2.5 percent as you can see at the bottom and as you have discussed. Ear pruritus, mouth edema, eye pruritus, lip swelling, and some of the other local effects including pharyngeal edema and swollen tongue.

Severe TEAEs were reported in 9.8 percent of the ORALAIR recipients and 11.9 percent of the placebo recipients. Those that were weighted towards the ORALAIR recipients were oral pruritus, mouth edema, throat irritation and dysphasia. Those were the ones that were considered severe.

Discontinuation due to related TEAE, 4.7 percent of the ORALAIR recipients, 1 percent of the placebo recipients. There was none that really stood out amongst the others. There were a number of reasons that the subjects withdrew including some of these local effects and effects that may -- most of them were local, but not all of

them.

As far as serious adverse events, there were two in our review. They were certainly related to ORALAIR. One application site reaction that was referred to as angioneurotic edema or severe local reaction on both of these occurred with first administration in the health setting. No epinephrine was used in these subjects in any of the subjects treated with ORALAIR as has been discussed.

Regarding children and adolescents, the total number of those who received the ORALAIR versus placebo was 154 versus 158. They were about evenly divided between those who are the adolescents 12 to 17 years of age or the children 5 to 11 years of age. The mean age amongst the groups were similar as was the incidence of asthma and the mean duration of exposure 150 days.

The most common treatment emergent adverse events were all pruritus, throat irritation, and mouth edema. You could see I think the standard constellation of other symptoms that were reported in greater than 2.5 percent of ORALAIR recipients at a higher frequency than the placebo group.

Those that were referred to as severe were reported in 17 of 154 subjects or 11 percent compared to 5.1 percent of placebo recipients. They included oral pruritus in four subjects and oral pharyngeal pain in two.

5.2 percent of these children and adolescents discontinued ORALAIR due to the adverse events, six due to oral pruritus and one due to chest discomfort. That is seven of the eight and 1.3 percent of the placebo recipients as you can see below.

Serious adverse events were reported in two children, one subject with asthma. The onset was day 124 after the first administration of ORALAIR and one subject had Burkitt's lymphoma. Neither of these was considered related to ORALAIR by the investigator or by the reviewer. No epinephrine was used in subjects who were treated with ORALAIR.

Regarding the post-marketing safety data after approval of ORALAIR in the European Union in 2008, there were two post-authorization observational studies in Germany. The first study included 808 adults and 91 children and adolescents. Mouth edema was the most frequently reported adverse events. The withdrawal rate was 9.5 percent. There were six serious adverse events including laryngeal and pharyngeal disorder. On day three, oral pruritus aggravation of Crohn's disease and lipid tongue swelling on day seven.

In study two, this was of children and adolescents. Throat irritation was the most frequent adverse event and the withdrawal rate again was about 9.2

percent. There were six serious adverse events including anaphylaxis in a ten-year-old boy with a previous medical history of bronchial asthma. He had lipidemia, itching of his hands. The day of therapy -- this was not specified, but there were no respiratory and circulatory findings reported. There was one episode of throat irritation with dyspnea and flushing and one episode of tongue edema with pharyngeal edema and dyspnea.

These are the post-marketing spontaneous reports. Again, please keep in mind that we are uncertain of what the denominator is of this. We are simply reporting this as the number of reports to the sponsor. What we most wanted to share with the committee was that there were six episodes of anaphylaxis within 20 minutes of the first dose, one episode on day nine. one episode five months after the first intake, and nine hours after the self-administration of the ORALAID, and one episode on day 30 several hours after the dose. As far as anaphylaxis in children and adolescents, there were two episodes within 20 minutes of the first dose, one on day seven, and one day 45, both of them pretty closely associated with those doses.

I wanted to discuss with you to show you a little bit a couple of these subjects, these children who had anaphylaxis after day one of therapy. One was a nine-year-

old male with oral and food allergies with well controlled intermittent asthma treated with antihistamines prior to self-administration of ORALAID. He did not get those antihistamines on the day that he experienced this event. On day seven, five to ten minutes after ORALAID, he had a swollen tongue, difficulty breathing, and he was treated with a beta-adrenergic and an antihistamine. But this continued to get worse. He had difficulty speaking and then he was treated with epinephrine and his symptoms resolved.

And then there was a ten-year-old female with multiple allergies and asthma requiring daily Salbutamol. On day 45, 30 minutes after her dose, she had face and tongue edema, cough, dyspnea and rash. She was treated with Salbutamol and prednisone. It was stated that she fully recovered within four days.

The severe laryngopharyngeal reactions in adults. There were five episodes within 20 minutes of the first dose. Two of those were within five minutes of the dose. One, 5.5 hours after the dose and two in which the time after intake was not documented. There was one episode on day three, five minutes after the dose, and one on day 12 immediately after the dose. This was proceeded by 11 days of itching of the tongue and throat edema. And then there was one episode each on day six and day 21.

The spontaneously reported severe adverse events. The severe laryngopharyngeal reactions. Three episodes on day one, two within five minutes of the dose. An 11-year-old male with throat irritation associated with the dose and severe symptoms on an unspecified day after that. And a 13-year-old female with cough after intake on day two who continued therapy. And on day four, 24 hours after the dose, presented with dyspnea cough and asthma. And then one episode on day nine, three minutes after the dose.

I have described for you the product. I have reviewed for you the product description, the proposed indication, the efficacy data that are of greatest interest to the agency, the safety data as we interpreted that, and those data that are most of interest to the agency and the post-marketing studies, two of which were studies and then the post-marketing survey for which we are uncertain of what the denominator is. We simply reported the number of events. That is all. Thank you.

Agenda Item: Questions

DR. NELSON: Thank you, Dr. Rabin. The floor is now open for questions.

DR. KELSO: In these studies, how are the placebo tablets blinded? Do they have a little histamine in them? How do you convince somebody that they are taking -- how would they not know they are taking a placebo tablet?

DR. NELSON: If the sponsor wouldn't mind answering that question, I would appreciate it. Thank you.

DR. ZELDIN: I believe the question was regarding to the study blind and how was blinding maintained.

DR. KELSO: Particularly in terms of the fact that I cannot imagine that somebody who is allergic to grass pollen who eats a tablet. We already know that huge numbers of people get at least a little mouth itching. How does the patient not know that they are getting placebo versus the active drug?

DR. ZELDIN: If I understand correctly, the question is was the blind maintained is essentially the point. The answer is and I think it is best answered by did the appearance or the experience of application site reactions seem to influence the patient's ability to assess the efficacy of their drug, their treatment. And the best place that we had to look at that was our first study, the VO34.04 study. There, we had a very similar rate of application site reactions reported in the three dose groups. You will recall that in that study, patients were randomized to placebo, 100 IR, 300 IR, 500 IR. They had a very similar rate of application site or adverse events reported across the three active treatment groups and yet they very well were able to distinguish between efficacy, which was observed in the 500 IR and 300 IR groups, but not

in the 100 IR group.

DR. KELSO: I think that does sort of partially answer the question, but I still think we are faced with the fact that the vast majority of the patients in all of these studies knew which group they were in.

DR. ZELDIN: In the US study, we actually looked specifically at this question to say did patients who reported an application site reaction or an adverse event. How did they grade their scores? Because one would think perhaps that if I took a drug and I got some tingle or I got some sense that I knew what I was taking that I might then believe that I am receiving active therapy and I might perceive that to be more effective. Does that make sense? I know what I am taking. I think I am getting the good stuff. I am going to feel better. In fact, it was not at all the case. In the US study, those patients who had such symptoms actually reported slightly worse symptom scores than those who did not report such symptoms.

We conclude based on these two studies and having looked really carefully at this because it was an area of interest and concern of course was that the blind was maintained and did not influence the patient's ability to properly assess the efficacy of their product, which was I think frankly we found very helpful and interesting and reassuring.

DR. NELSON: Thank you for addressing that question. Before we get back to questions for Dr. Rabin since you are here, perhaps you can describe for the audience and the panel what the composition of the placebo actually was and did it vary amongst these trials.

DR. ZELDIN: Perhaps Dr. Moingeon could describe it better than I. Let me call Dr. Moingeon to ensure we get that exactly right.

DR. MOINGEON: Good afternoon ladies and gentlemen and members of the advisory board. My name is Philippe Moingeon. I am the head of research and pharmaceutical development. Back to your question. The placebo only contained the excipients. We used very conventional excipients such as silica, lactose and the exipients we have as well in the active treatment.

DR. ZELDIN: And I believe you asked. The question was and were they the same throughout the program and the answer is yes. There was also a very interesting comment about was there histamine put into the tablet. That is a really interesting question. Unfortunately, when you do that, histamine does not have any reaction when administered orally. It is something that has been discussed. I reviewed the scientific literature on this point and it does not enable us to successfully or more successfully blind sublingual immunotherapy. That is a

great question.

DR. NELSON: Thank you.

DR. DAVIS: I specifically have a question and concern about pediatric patients and the lack of safety data in the pediatric population. There was no direct dosing in that population, but there were some significantly adverse events in pediatric patients that got 100 IR in their first dose. I wanted to find out. Did you find any differences in the adverse events in the pediatric population with the 100, 200, and 300 dosing?

DR. ZELDIN: In the development program and also throughout our post-marketing experience, every child has taken -- it started with 100 and gone on to 200 and then gone on to 300. The rare events as Dr. Bons shared with you, we have a significant experience across this now five years of being on the market. We estimate over 37,000 children treated. The first day would seem to be the most critical day. Most concerning adverse events, the kinds that you and I as clinicians would be most worried about occur on the first day. There are rare events as Dr. Rabin shared and Dr. Bons that occurred subsequently.

I think that is exactly why we propose the pharmacovigilance plan that Dr. Bons shared with you to make sure that patients are all aware that allergen immunotherapy whether subcutaneous of sublingual can cause

serious adverse events with our product. I think it is certainly fair to say that most occur on day one and that is why we want patients to be sitting in that doc's office under observation for at least 30 minutes. But certainly rare events do occur subsequently and they need to know the signs and symptoms of those events, how to address those events, and certainly to not restart therapy or continue therapy after experiencing such an event. That is the conglomeration that we think is very important to communicate to the clinical community and to the patient population.

DR. DAVIS: Just a follow up question because I did see that some of those cases -- actually, one of the girls actually had a history of dust mite allergy. My understanding was that patients that had house dust mite allergy actually were excluded. If you could clarify why some of the patients that had these adverse events actually had other environmental and some perennial allergens. And if you could also comment on how many perennial allergens. What was the range of perennial allergens that you actually tested in these patients?

DR. ZELDIN: I think the answer to your first question is I think there is a difference between the clinical development program, study view 52.06 and that study as we discussed earlier. If a patient was dust mite

allergic, not just skin test positive, but also had clinical evidence of dust mite allergy, they would not have been randomized to the trial. In the real life experience, which post-authorization safety study, and certainly as we are now being used on the market in Europe, patients come with their individual histories and have used the product as this young girl did with a history of dust mite allergy. When we get such a report, we try to solicit as much information as we can about the report so that we can best understand what does this patient have and ultimately pharmacovigilance response of course is is there some signal. Is there something that we can identify some sub-population where we should be exquisitely careful or extra careful and communicate that to the scientific community and to the patient community?

DR. DAVIS: I just want to make a comment with regard to that because when this product if it gets into the general market and is given to patients that actually do not have sole grass allergy, but do have other allergens then the safety may be compromised. I do not know if you have some comments about that as well as the fact that in food oral immunotherapy trials, other factors such as exercise or menstrual period can actually alter the adverse events. If you could just comment about did you see that in post-marketing reports where the tablets were tolerated

and then were not tolerated later because of other external factors. How do you propose this product really should be used in that setting and how providers should be warned?

DR. ZELDIN: I would be happy to. I think the answer to the question regarding the post-marketing experience now over these last five years is that we have an aggressive pharmacovigilance and we have not to date identified a subpopulation or a special group where we should based on our data be specifically careful or concerned. I think David Golden might want to comment on this. I think we have discussed this as professional colleagues. Who might we want to be especially careful with in general in administering allergen immunotherapy including sublingual. David, do you want to comment on that?

DR. GOLDEN: I would be happy to. Just as a clinician with some years of experience, I think we will all agree that there is common sense involved here. There is clinical judgment. When we prescribe immunotherapy of any kind, there are clearly patients who have evidence of reactivity, risk factors. It would be of special importance to the prescribing clinician to consider as much as it is a known risk factor for adverse events with immunotherapy and anaphylaxis in general, whether patients with a history of any anaphylaxis, I guess that -- one of

the risk factors for anaphylaxis is prior anaphylaxis of any kind. Patients with known anaphylaxis to virtually anything. I am not saying they should be excluded. I do not think that would be a fair statement either. But the recognition of potential risk factors would be important. Again, we do not exclude such patients from subcutaneous immunotherapy, but the clinician needs to be aware of the patient they are dealing with, the potential risk factors, to counsel the patients accordingly and to discuss the potential risks and the therapeutic decision making process.

DR. ZELDIN: I certainly wholeheartedly agree with that. In our proposed prescribing information that we have submitted to the agency, we have identified clearly the patients with uncontrolled asthma, the patients that asthma should be controlled when taking this medication consistent with the practice parameters. Patients who require beta blockers. We need to be attentive to patients with certain past medical histories and to require certain medications and weigh the risk benefit in the individual patient as to whether it is the appropriate way to go. We are trying to be very proactive in addressing these sorts of concerns.

DR. DAVIS: Just a follow up comment on that. It sounds like you said that the asthma -- the patients were

well controlled, but it sounds like really the inclusion criteria was to take patients who only had mild intermittent asthma.

DR. ZELDIN: That is absolutely the case. We did not study a population of patients requiring anything other than inhaled beta2-agonist. These were what we would call patients with intermittent asthma. Absolutely that is the case. And the reason for that is precisely because it is what is in the FDA guidance for the population of patients that are appropriate to be studied in studies of immunotherapy in general. It is exactly consistent with the guidelines. We do think it is important to communicate very proactively that patients with uncontrolled asthma are not the patients who should be receiving this therapy. We are very transparently communicating that consistent with the guidelines we did not study patients who required anything but inhaled beta 2 agonist or intermittent asthmatics.

DR. NELSON: Great discussion. I am sure during the safety discussion this afternoon, we will get into the version of that gap between intermittent asthma and uncontrolled asthma. There are a couple of other categories that we probably need to discuss.

Are there any additional questions regarding the FDA presentation? I believe Dr. Apter and Dr. Riedl had

one.

DR. APTER: You mentioned that the five-year study from Europe, 5306 was a five-year study, and you gave the results of observation of years four and five. Could you review either sponsor or Dr. Rabin? Is there other data on observation of patients after discontinuation?

DR. RABIN: We have essentially what we presented to you, which was the five-year study of subjects who were pretreated for two months before the anticipated start of the grass pollen season and the subjects who were treated four months before the anticipated start of grass pollen season and the combined scores of those sets of subjects along with the placebo. That those are the only data that we are aware of.

DR. APTER: It is very little data and it does not show -- so far there is no data showing a prolonged effect after discontinuation.

DR. ZELDIN: I missed the last words that you said.

DR. APTER: My understanding is that there is very little data so far on patients who have had three years of sublingual immunotherapy to grasp and there is very little data showing any prolonged benefit the way there is some data on prolonged benefit from subcu immunotherapy.

DR. ZELDIN: We have the study that we shared and Dr. Rabin shared, this VO53 study, 633 patients, randomized to either placebo, two month pre, co-seasonal four month pre and co-seasonal. The study was designed -- I would be happy to show it, but I can certainly speak to it. The study was designed with a three-year primary efficacy end point. The objective of the study to confirm the sustained effect, which is during the treatment period and also to look at the post-treatment effect. The study was designed. It is a four-year study. I will put it up just to remind the committee. Here are the data.

DR. DAVIS: I did have a question about the combined score for year five for the placebo. It seems that there was a discrepancy on the slide. It was .38. But then on the presentation that we just saw, it was .56. If you could just clarify.

DR. ZELDIN: If you wouldn’t mind, let’s take a look at that at the break and come back and address that. I just need to see the other numbers just to see if I can help to explain it.

Can I just address your comment? This was a three-year of treatment study. The study was planned to have a fourth year post-treatment observation. We saw evidence suggestive of a post-treatment benefit in this study. A fifth year was added. Again, we saw evidence

suggestive of a post-treatment benefit. I think your comment about the sample size is well taken. I think that that is why we are specifically saying we think these data are suggestive because they are not in tens of thousands of patients. That is a very fair point.

I think there is one additional point that is worth knowing on the slide. I think the visual is the most striking. What you see is a remarkable and continued improvement in the placebo group from one year to the next. We get down to the .35, .31, and .27. We are getting to a very low level of symptoms in the active group beginning with the second year. But that placebo looks like it is just really marvelous. There is a reason for that. We have looked at these data very carefully. And the reason is that each year, year after year and especially between years four and five, the people who withdrew from the study in the placebo group took with them a higher symptom score than did those in the active group. Indeed it is not that placebo is getting more potent over the years, but that the sick patients in the placebo group left and took with them higher symptom scores than did those in the active group who left. We see a natural narrowing of the percentage difference.

And of course, as Dr. Rabin I think well pointed out, we also see a widening of the confidence interval

because we have fewer patients from the beginning of the study to the end. It is a bit of a catch 22, but I think the important thing for the committee is to just share everything as Ron has and I am hoping to do with you just so that you can understand the data as we have them.

DR. RABIN: Dr. Davis, the error that you astutely pointed out, the point .38 is the correct number.

DR. RIEDL: Just a quick question to clarify in my own mind. I might ask Dr. Rabin first and then the sponsor can add. The episodes of anaphylaxis and/or severe oropharyngeal reactions that the agency reviewed in the data, it appears from our view the preponderance happened on day one from the collective data. Is it your understanding that that day one was always a dose of 100 IR? Because in the different studies there has been the 100 used on day one and the 300 used on day one and a small proportion. My question relates to the dose that induces those day one severe reactions.

DR. RABIN: My understanding is that all the licensing outside -- all the licensing, all the current licensing includes the ramp up. But the clinical studies in adults did not include the ramp up. In answer to your question, my understanding is all these day one reactions were to the 100 IR dose that were described at least in the post-marketing studies and in the children in the clinical

development program, but not the adults in the clinical development program.

DR. ZELDIN: I think Dr. Rabin has nailed it exactly right. For the post-authorization safety studies, for the post-marketing self-reporting, those were always 100 IR administered on day one. As he well stated for the pediatric study and for that first study in Europe, VO34.04, those two studies were with the ramp up. The other studies, the US study, the long-term study, that two-month study looking at an alternate regimen, those were with direct administration of 300 IR just to make sure we are all on the same page.

DR. SAPER: I had a couple of questions about the oral dissolving tablet. Can either Dr. Rabin or Dr. Zeldin address how quickly is the dissolution? How long do you have to keep it under the tongue? I am speaking to a possibility. Could you have swallowed the tablet or is the dissolution really pretty prompt? Then I have some follow-up questions.

DR. ZELDIN: In our labeling, we advise the patient to keep the tablet under the tongue for at least a minute and through full dissolution. Philippe is much more knowledgeable on this point. Dr. Moingeon, would you like to just make sure that we get it exactly right?

DR. MOINGEON: Yes. Complete dissolution is

obtained within less than three minutes. This is basically the time it takes to have a full release of the allergen from the excipients and then binding of the allergen to the mucosa that will subsequently facilitate capture by immune sets.

After those three minutes you can then swallow. This is the so-called sublingual swallow procedure, which has been used throughout the clinical development program.

DR. SAPER: There was a possibility that after you hold it under your tongue, there still is a tablet that you swallow, correct? Is that what you just said?

DR. ZELDIN: My understanding is that the instructions to patients are to keep the tablet under the tongue for at least a minute and until complete dissolution. That is exactly as we say it in our European labeling and as we would propose to have it used and in the US as well.

DR. SAPER: To clarify what I am hearing is that if you do not hold the tablet under your tongue for a minute, you will have a tablet that you can swallow. It is not completely dissolved. Is that correct?

DR. ZELDIN: I think based on the dissolution time, you would still have a big of a fragment.

DR. SAPER: The reason that I am asking that is addressing the GI side effects. I believe that I would

like some more attention paid to the number one difference in reported side effects that you see that is different between actively treated and placebo are actually the GI side effects. Now part of those you are including pruritus. But within there, it seems like -- in the context that there are very few TEAEs, among those there is just proportionately GI and among those GI there are significant percentage of those GI, which I know are small in number that are things like abdominal pain, vomiting. You have a child who discontinued because of chest discomfort. You might think of that as esophageal.

Dr. Lierl asked the question about eosinophilic esophagitis. There is actually a published case report just from this past October. A 44-year-old woman. It was Birch sublingual immunotherapy who had biopsy-proven EOE, that seemed to be related to SLIT. And it did resolve afterwards. She was subjected to endoscopy and biopsy. There is an undercurrent of concern that is an eosinophilic esophageal disorders may be a risk of sublingual immunotherapy. And some of those may not be simply things that happen right at the time of tablet administration. Those would be a slower look, not just the acute GI effects that Dr. Riedl was concerned about because we know those are part of acute anaphylaxis. I am talking more of long-term, safety signal. And then the sub of that is what

about children with food allergies. Would they be more at risk?

DR. ZELDIN: Would it be helpful to share our experience in the clinical development program with respect to gastrointestinal disorders specifically? I think it would. Here is a slide that addresses this very point. These were the events that mapped to the system organ class gastrointestinal disorders, more than 2 percent of patients, and began higher incidents. There were some that go the other way, but these are the ones with the higher incidents in the active group versus placebo. As you well said, the most common ones are the oral pruritus, the edema mouth, the tongue pruritus, the lip and tongue edema. But there were rare cases in both the active and placebo group of upper abdominal pain. This is the comprehensive list of any of them that occurred in more than 2 percent. I hope it contextualizes our experience.

DR. SAPER: That is just one of the tables that were in our briefing documents. There were some that actually had -- I think, Dr. Rabin, you had in one of your slides. There was also vomiting. It was number two or three and there was abdominal pain. I do not remember which table number this is. It looks like it is table five. There is a table 3.3 that had GI facts. Table 38. There were other tables that really did speak to numbers of

patients with the sorts of symptoms that I was concerned about.

I am not trying to imply that this seems to be a frequent adverse effect. The question is that post-marketing. If you do not pay attention to the possibility of eosinophilic esophagitis because that could be hidden among many patients who have a diagnosis of gastroesophageal reflux disease and hidden within that we find the population with EOE. I am not seeing a lot of attention paid to what seems to be one of the number one areas of concern for safety going forward.

DR. ZELDIN: I really appreciate that comment. I am not an expert at eosinophilic esophagitis. But my understanding would be that symptoms would persist after treatment discontinuation and that just has not been our experience. I just may not understand.

DR. SAPER: I do not think necessarily. There is a lot of concern that there can be more seasonal eosinophilic esophagitis. The question is there could be seasonally eosinophilic esophagitis and this is all preliminary. Are you still at risk of having esophageal remodeling strictures developing in dysphasia? I will leave it at that. There are some bodies of evidence. Nothing is really there. Eosinophilic esophagitis is now only definitively diagnosed by endoscopy and biopsy. Some

people have a higher bar to subject to their patients who have it.

My other question would be on the pediatric patients. We see them all grouped. How many five year olds are there and how many five year olds are going to hold the tablet underneath their tongue? I was involved in an investigator initiated sublingual immunotherapy. Five year olds just do not like the taste. We call it the singing medicines so they would not swallow. You had to get them to participate. And your tablet -- you want to hold it for a minute. We had our patients sing either the ABCs once or happy birthday twice. I do not think that is a minute.

DR. ZELDIN: If I could answer the question. The experience in the clinical development program. We know that there are 139 kids in the VO52 study. That was the pediatric study. In the actively treated groups of the total number of 1500 patients across the program, there were 67 adolescents. That is 11 to 17. And 87 children 5 to 11. I do not have with me the specific breakdown below that. I am sorry. We could certainly look it up and see if we could share it with you after the break.

DR. SAPER: I think that would be of interest so we can understand whether five year olds actually can comply with this just because of mechanics and age, not

because of specific safety.

DR. NELSON: I think we are all interested in the stratification by age. I believe Dr. Webber had a comment.

DR. WEBER: A different point. Standard of care with subcutaneous immunotherapy. If someone had an adverse reaction, that does not stop the immunotherapy. Most of us go on and continue to give repeated injections thereafter.

Now, in the protocols, pretty much if there was an adverse event, it was stopped. Now, what my question is is in the post-marketing data, if you have it, presumably there are numerous patients or subjects who even after an adverse event will restart the sublingual immunotherapy. Is there any data on the prevalence of repeated adverse reactions after an additional reaction and then restarting or continuing the immunotherapy? Whoever can answer that.

DR. ZELDIN: I want to make sure I understand. I think that you are suggesting that in the clinical development program, patients who experienced treatment emergent adverse events discontinued therapy. In both the active and placebo groups, the majority of patients reported some treatment emergent adverse event over the treatment period, over that pre and co-seasonal. And a small proportion, only 5 percent in the active group and 1.2 percent in the placebo group discontinued treatment. That is just a point of clarification.

But then I think your second question was about in the post-marketing experience, do patients stop? I think the most relevant perhaps are from the post-authorization safety study. I can share this with you just to highlight the point. Where I was headed, Dr. Weber, was just most folks had something over a five-month period. It is the bottom line, 76 percent had something in the active group, nearly 70 in the placebo group. But then we had the 5 percent who actually withdrew in the active group and 1 percent in the placebo. Most patients, as we talked about earlier, play through.

I think that is certainly also the case in the post-marketing experience. In the post-authorization safety study, which was just a natural exposure study in Germany, 1700 odd patients, somewhat higher proportion stopped, but it was under 10 percent. Our gestalt sense of it is between 5 and 10 percent of patients are not going to like the tingle, not going to like the itch or have more serious events that result in their discontinuing therapy. That is the overall sense of it for us.

DR. NELSON: Dr. Weber, I had a similar question that I will pose now, but defer the answer until we get into the discussion phase. That is, among the litany of adverse events that have been observed, which ones as you have counseled physicians to administer this therapy would

recommend the possibility of entertaining or re-challenging continuation of therapy as opposed to stopping specifically a different way of asking that question from a practical standpoint.

I will take the chair's prerogative and the last question for this session by asking Dr. Rabin. I noted that during the beta for the adults and children the mean duration of exposure was somewhere in the 130 to 150 range, which seems a little short for four months of pre-therapy and all the way through the season. I wonder if either of you would mind commenting on whether that represents inclusion of the two-month pre-treatment or the dose escalation data or some other reason why they did not extend through the season and have a higher average.

DR. ZELDIN: Ron, you can answer if you would like. Indeed, in the VO60 trial, which was that two-month pre and co-seasonal, there were a number of adolescents who participated in that trial as well. That is what shortens the overall exposure. You have it exactly right.

DR. RABIN: I think the other issue, Dr. Nelson, is that probably in that slide as many times as we have gone over it probably those are not normally distributed data and we probably should have presented the mean and median because you do have some withdrawals on day one as we have discussed.

DR. NELSON: Fair enough. Next up in the agenda is the open public hearing. I will turn it over to Mr. Jehn.

Agenda Item: Open Public Hearing

MR. JEHN: Pre-meeting, the FDA did not receive any request to speak in the open hearing. But that said, is there anybody in the audience today that does? Dr. Nelson, it does not appear that anybody wishes to speak.

DR. NELSON: That brings us quickly back up to speed and perhaps on time as a matter of fact. We now head into the lunch hour. I would advise the committee members that an express lane has been set up for you so that you are able to get your lunch. It is in an entryway behind the kiosk, behind this front entrance. Then down the hall to the left, Room 1506. 1506 is open to you to sit there. It has been reserved for your purpose. We will adjourn now until 2 p.m.

(Whereupon, a luncheon recess was taken.)

A F T E R N O O N S E S S I O N

Agenda Item: Committee Discussion and Vote

DR. NELSON: Good afternoon ladies and gentlemen. Welcome back from lunch. We will reconvene now. Scheduled for this afternoon is the committee discussion and vote. What I will do first is run through the questions that have been put forth before the committee just very quickly. I will read them verbatim. You see here the first one regarding available data to support the efficacy of ORALAIR. The second one is a vote concerning whether the available data are adequate to support the safety of ORALAIR. And the third and fourth are discussion items. The third, please discuss whether the available data to support the continued efficacy of ORALAIR through one or two years following the course of treatment of three seasons. And four, comment on what additional studies if any should be conducted post-licensure.

We have discussed briefly at lunch just the strategy for how to conduct this discussion and vote this afternoon. I think we have come to a consensus that we will continue with general questions. It may overlap between the different questions before the group. And then we will launch through consecutively each of the four questions and items so that our team from the FDA can capture the input from the committee.

I will now open it up and ask a representative from the sponsor to also join us at one of the microphones.

DR. CASTELLS: I would like to reflect before we go deeper into safety questions about the mechanisms by which we think this is working just from a mechanistic standpoint. This is actually not like classical immunotherapy because we are not building up. After several months or weeks, we are not just adjusting to a dose. And it is also not what we desensitization because desensitization -- it would be like one day. We do that for hymenoptera venom and then we are able to induce safely doses. Here, I have observed that after seven days, after 45 days, you can still have very severe anaphylactic reactions.

And your data about the IgE4 that there was some IgE4, which might think that you have created some regulatory T cells is intriguing. There is like a hybrid in which we have -- it is not really a vaccination and it is not really a desensitization. We come up with either 100 or 300 and we just give it from the bat. And then we expect the patients to do either a T cell tolerance or to be desensitized.

I would like us to put that in prospect and reflect that this might have an impact in safety. What do we say to patients who start to have that pruritus and

mouth pruritus? Is it something that we should say to them just suck it up and continue or is it something that we are saying this might be an anaphylactic process? Just open our minds towards that.

And I guess you may not have other mechanistic studies to light some liking to that, but it might be something to think in the future.

DR. ZELDIN: Let me ask Dr. Philippe Moingeon to address the mechanistic aspects and maybe we can come back and speak a bit more.

DR. MOINGEON: We have actually some idealism of how the treatment is working. Basically, what happens is discussed very briefly this morning by Professor Wahn. The allergen is captured very quickly in the upper layers of the oral mucosa by dendritic cells. Now, the interesting thing is the dendritic cells in the mouth are very special. They do produce enteric content and they do produce TGF beta and thus they will drive the immune responses in the draining lymph nodes towards TH1 and regulatory T cell responses and thus we do not speak enough about desensitization per se but more immune deviation. Remember those patients have established TH2 responses and there is immune deviation towards TH1. That is the first part. And the second component is the induction of regulatory T cells. This we call immunosuppression.

We have actually conducted a number of biological analyses in support of clinical studies. As Dr. Zeldin has mentioned, we have shown induction on a regular basis of specific IgG4s, which for us is just a sign of immunological activity. But you cannot relate clinical benefit to the induction of tolerance and induction of IgG4.

What we have seen which is quite interesting, is an induction of DC regs, regulatory dendritic cells, which we can detect in the blood. This is of course as of today, ongoing research. But this is basically as of today the immune change that we have seen in the blood, which is the best correlated events with clinical benefit. And as per your suggestion, investing a lot of time and effort to complement those studies.

DR. CASTELLS: It seemed that at two months you did not have this kind of immunomodulatory mechanism. You needed four months to induce any particular changes. Is this what correlates?

DR. MOINGEON: Not exactly. Actually, we see those immunomodulatory mechanisms starting from two months. We did not look before. But again, before having a clinical benefit, we may have to build up those regulatory immune responses. Maybe there is a differential in the timeline. I guess we need to illicit those appropriate

immune responses and this will take several weeks. It is very hard to say how much time it takes. I think it is very consistent with the fact that we have a well-established clinical benefit after four months of immunotherapy.

DR. CASTELLS: Have you been able to do any biopsies of the patients or is this something that -- patients who have had reactions or in patients who have had any difficulty with that. Have you noted any hyperplasia of mass cells or anything in the mucosa or have you measured tryptase in the saliva or anything like that?

DR. MOINGEON: We actually have conducted some biopsies in the context of clinical studies locally to look at immunological changes in the context of immunotherapy. But we do not have the results right now. Those studies are ongoing.

DR. ZELDIN: Dr. Castells, you mentioned also -- I believe part of your question was around time of onset of effect. I think the study that provides the most insight with respect of time of onset might be the chamber study that has that advantage of being in a pure controlled environment. And there as you recall from the initial presentation, we did a challenge at baseline at one week, one month, two months, and four months. Can I show the graph that shows over the four months the separation? The

short answer is that in that study, we saw separation between active treatment and placebo beginning after just the first month of the first month's challenge and continue to widen over the second month's challenge and then was widest at the fourth month. It is just a statistically significant difference beginning after just four weeks of therapy that widened over the subsequent months of treatment.

DR. SAPER: Just a follow up on that. If you overlay the natural pollen load, in the study that just had two months since it was an environmental chamber, was it just less of a pollen season so that you could not see separation of treatment effect?

DR. ZELDIN: The question for the group because I would love to show a slide to that very point. We actually looked carefully at why in the VO60.08 study, that alternate regimen study that you are describing. Why was that study clearly not successful and yet in the long-term study we had an arm that appeared to show efficacy with that two-month administration regimen? And there was absolutely nothing that we could discern. The populations were similar on all of the principal criteria for enrollment and the exposure, the pollen season was actually quite consistent with that of our other studies. The take home that we took from that study was the study is valid

and we have to take the data as they came. That is why we have sought for and received to date approval for the four-month pre-season and co-seasonal regimen because in that study consistently study after study after study we have had a favorable result. And in this alternate regimen study, we did not. It is exactly the question that we explored quite carefully.

DR. NELSON: A quick follow on for me on that very same point. Given three consecutive pre- and co-seasonal treatments, is there any thought given that perhaps during seasons two and three you will not need four months of lead up time to see the achieved response during the season itself if indeed this is a truly disease modifying regimen?

DR. ZELDIN: We have not explored that question. It is a very interesting question. Our study, as you saw, was one that was looked at, but it is a very thought provoking question.

DR. KELSO: I have four questions. I think three are very brief. 300 IRs equals how many BAUs?

DR. ZELDIN: I can tell you in micrograms of major allergen that is group five. It is about 20 micrograms. I believe, but Philippe will confirm because we are just establishing --

DR. KELSO: Once in your presentation and also in

the book it says that we will be told how many BAUs equal how many IRs.

DR. RABIN: Perhaps I can address that. I do not think they know because we have not told them. We have had some internal discussion as to how we are going to quantify this with BAUs given the fact that it is a mixed product. What we have decided on is that we are just going to equate it to Timothy BAUs. Where it ends up coming out in a competitive analyzer, which is how we measure BAU which is the surrogate measurement for BAU that we use for all the standardized grass products is it comes out that 100 IR is roughly 3000 and 300 IR is roughly 9000. That is kind of where we are going. We still have to do some internal validation assays. We still have to figure out some things internally. That is probably where the numbers are going to fall out.

DR. KELSO: Am I correct that all of the data that was presented, none of it was presented with an intention to treat analysis. Is that correct? When people dropped out, they are not counted anymore.

DR. RABIN: Perhaps the statisticians can speak really very precisely to this. The data that I presented is my understanding is what is called the full analysis set, which for all practical purposes is an intention to treat analysis. There are some subtle differences that I

cannot remember right now. But essentially, it is an ITT analysis.

DR. KELSO: My understanding of that is there may be differences that people dropped out and that have to do with the final outcome. For people, for example, who are being treated and discontinued therapy then did we continue to measure their outcome over time as if they had received therapy. It seemed that they had not because the ends kept getting smaller. It seemed like when people dropped out for whatever reason, that was just the end of their assessment.

DR. ZELDIN: Dr. Kelso, what we shared with you with respect to the full analysis for each study as I shared with you that each group, the active and placebo groups were balanced. Those all spoke to the efficacy analysis in the full analysis set. Armelle Montagut is head of biometry. Let me ask Armelle just to make sure that this point is well addressed.

DR. MONTAGUT: In data, to do a real ITT analysis is difficult because patients are randomized four months before the start of the pollen season. They can be assessed only during the pollen season. This is a set of patients who are randomized and who have at least one evaluation efficacy. That shows a drop out cannot be included in this analysis for each individual study. We

have contacted different scientific analysis in order to assess the impact of the drop out of our analysis(?) and sensitivity of the disease using a single mutation(?) by replacing the missing score by the mean score of the opposite group. For each study, we conducted sensitivity analysis and they led to similar statistical conclusions.

DR. KELSO: I guess what I am hearing is that in fact this is not an intention to treat analysis, but that assessments were made to determine whether or not the loss of data from people who dropped out impacted the final result of your assessment.

DR. ZELDIN: I think I understand the question clearly. Each patient who reported a symptom score and recorded their medication use during the pollen period was included in the data set and every day of such data was recorded.

DR. KELSO: And patients who dropped out or who discontinued therapy for whatever reason they continued to report their data.

DR. ZELDIN: The data that could be included were only the data for the patients who are on therapy and recorded symptom scores and rescue medication scores.

DR. KELSO: If I am taking whatever and turned out to be placebo or the real drug and I say this makes my mouth itch. I do not want to be in your study. I do not

want to do this anymore. You do not have to keep taking the tablets. We want you to keep recording your symptom scores or they no longer provided data after that point.

DR. ZELDIN: The latter is the case. Then we did sensitivity analyses to address patients who dropped out before the onset of the pollen season to ensure that indeed they were captured and that the data remained robust and that was indeed the case as Montagut just shared.

DR. KELSO: One of the questions was about oral lesions. Is there some provision where people who just had their tooth extracted or bit their cheek or something where they might suck on this thing and have an intravascular absorption of the drug. Is there some thought about that?

DR. ZELDIN: Actually, it is addressed in our European labeling and our labeling throughout the rest of the world. Anyone who has such an open lesion and we actually specify after dental extraction or dental procedure. We ask them to hold the therapy, to hold treatment, to not take the tablet until their mouth is healed.

DR. KELSO: And then finally, I think you may have tried to answer was -- with the five studies that you showed where it looked like there were three where it worked a lot better than the other two. There is nothing else that could be discovered about what was different

about those two studies to suggest why it worked less well in those two studies compared to the other three.

DR. ZELDIN: We did a number of efficacy studies, natural field included among them. Dr. Rabin showed the two-month pre and co-seasonal.

DR. KELSO: I think it is your final summary slide where it looks like there are five studies, three of them -- the two on the bottom. The arrows go up and cross the 10 percent line. Is there something identifiable that was different about why those studies appeared to show --

DR. ZELDIN: Certainly, one of them. Ron, you can answer it. But one of them was with a regimen for which we are not seeking approval. That was the two-month pre and co-seasonal regimen. Dr. Rabin gave a very comprehensive presentation and he included that study among them. But that is not a regimen for which we are seeking approval. I think that explains that one.

Ron, did you want to comment?

DR. RABIN: I guess it depends whether your question is satisfied.

DR. KELSO: You had in fact answered. You could not tell if there was anything different about -- the pollen counts were just as high. There was not any other identifiable explanation about why it worked.

DR. RABIN: Certainly, we did not identify

anything in our review. That is why we requested simply that the chamber study -- it appeared to us that the chamber study would clarify some issues and we are requesting that the committee look at the totality of the data.

DR. ZELDIN: I can show you, Dr. Kelso, the data all looking through the same prism of the daily combined score. I think what resonates most here is the consistency of effect. Here we have VO34.04, the European study, the pediatric study, the long-term study, and then finally the US study all with a daily combined score. I think the point that is different on this slide compared to the one that Dr. Rabin showed was here for the long-term study. We are showing the primary efficacy period, which for the long-term study was pre-specified as year three and Dr. Rabin showed the year one data. We are showing you data for the primary efficacy end point, European, pediatric, long-term and US. Is that helpful?

DR. SAPER: I have one other safety question. When you look at trying to do oral tolerance for foods, one of the things I have noticed is an increase signal in anaphylaxis during times of fever. Especially in the pediatric studies, you noted that there were more undercurrent viral illnesses. Did you notice anything or have any recommendations or data to advise regarding if a

patient has a febrile illness do they suspend treatment during that time?

DR. ZELDIN: I would ask Dr. Bons. Do we have anything from our pharmacovigilance experience to be able to comment on that? In our clinical data, in our post-authorization safety studies, we had nothing that would provide insight there. Nothing from pharmacovigilance.

DR. SAPER: Did you have those numbers on the granular data on the breakdown of ages?

DR. ZELDIN: Yes, we do. I was hoping you would ask. Can we please provide Dr. Saper with the specifics regarding enrollment in our pediatric study? This is the age distribution in our pediatric trial. It is actually not percent. I am sorry. But it is actually actual numbers. We thought that would be more helpful. You see by year.

I should point out that you see one patient who is enrolled at four years of age. Enrollment was at four years of age, but the patient did not receive study therapy until the child turned five years of age. There was no child treated under five years of age.

DR. SAPER: Did these children complete the study or did they drop out? Do you have any data on that?

DR. ZELDIN: We have overall data. I do not have it granularly by age. We also had of course a pretty

significant experience in the post-authorization safety study. I would be happy to share that with you as well. Dr. Bons, I think, shared this earlier. We had 829 patients treated with ORALAIR, 457 children, 372 adolescents. The common adverse reactions as you see are throat irritation, oral -- oral pruritus and mouth edema. And in this study, we had about a 4 or 5 percent dropout rate in the clinical development program in the active group. Here, it was somewhat higher. We talked about the fact that there is no anaphylaxis or severe laryngopharyngeal reactions in this study.

DR. NELSON: What were the instructions for administration to the children? For example, were they allowed to self-administer or were they required to be given by a parent or an adult during the study?

DR. ZELDIN: My understanding is that it was dependent on age and the younger kids. The parents would help out. As it was commented earlier, getting a five year old to do this just right can be a challenge with any tablet.

DR. RIEDL: Relevant to the questions that we are going to be asked to vote on, do you have similar data for the elderly population over the age of 65?

DR. ZELDIN: Our clinical development program enrolled patients up to age 65. The US study was 18 to 65.

We do not have clinical data from a randomized controlled trial in patients older than 65 years of age. There is some experience in the post-marketing, but we do not have a denominator that we could easily share with you.

DR. CASTELLS: How about clarification or maybe you already talked about that? In food allergy, we see that asthma is a factor that aggravates reactions. As in overall, did you feel that asthma in either children or adults was a factor that predicted a reaction or the severity of the reactions? Because it is important that we decide here when we answer the questions, would we give an EpiPen to those people? I feel strongly that in the American population, we need to make that distinction. Do they need to carry an EpiPen and are we making this recombination here today? I would like to see if there is a factor that would be able to single out those patients that would be more prone to reaction or if asthma in itself would be the factor that would determine the severity. You do not call it anaphylaxis. I call it an anaphylaxis. It is a little bit different. When somebody coughs and is short of breath, I call it an anaphylaxis if there are itchy palms associated with that like two organ systems. But I wonder if you had any overall globally. I know that study that you showed that 36 percent of the kids had asthma, 9 percent withdrew from the study. I am not really

sure that we know why where asthma involving that or not.

DR. ZELDIN: Generally, the withdrawals were for local application site reactions. They were not related to asthma. If we could share the slide from Brigitte's presentation earlier from the clinical development program. Reports of asthma. Asthma as adverse events in the clinical development program were reported at a similar rate in actively treated patients and placebo treated patients. And the tolerability profile in those with and without asthma was absolutely super imposable. If anything, we found the clinical experience in the 1500 plus patients treated, 425 of who had asthma, to be very reassuring. We think we can say with confidence that this product does not cause a worsening of asthma. In fact, as I shared with you earlier, with respect to courses of oral corticosteroids as treatment for asthma exacerbations, there were significantly fewer in the actively treated group than the placebo treated group.

DR. CASTELLS: I understand clearly that distinction. When you analyzed the people who had anaphylaxis, do you find that the people who had anaphylaxis had asthma or whatever you call it, the adverse event laryngopharyngeal -- whatever name.

DR. ZELDIN: We are dealing with a post-marketing surveillance experience. There is a selection bias,

recording bias that is hard to address with a simple answer and that is the challenge that I face. I would ask Dr. Bons to comment. Was there any larger representation in a group than in any other?

DR. BONS: What I can say is that we did not have any isolated cases of asthma exacerbation or asthma attack or asthma crisis in our post-marketing surveillance database. After that, it would be extremely hazardous to say today taking the continuous reports and making a relation of asthma in the past medical history with the case we have received. It does not reflect of course the population --

DR. WEBER: With one of my questions earlier about reactions, you pointed out that numerous subjects did have some reactions and persevered in the study. Trying to look at correlations with SKIT, we know that systemic reactions to SKIT are not predicted by the presence of local reactions. If we look at some mouth symptoms as the equivalent of a large local reaction, do you have any data that shows that those mouth symptoms were more likely to occur in people who then had a later more dramatic adverse reaction or not?

DR. ZELDIN: We do not have anything definitive in that regard. Those application site reactions were quite common. Again, it is hard to take that next step and

say that predisposes the patient to a more severe reaction. If 60, 70 percent of patients had some sort of reaction, the chances that one of them would go on to be one of the -- we had two in our clinical development program who had a serious drug-related treatment emergent adverse event simply by the odds would suggest that they would have had some sort of application site reaction. I will remind you of course that those two patients had their reaction on the first day. It was quick and done.

DR. NELSON: What about the more severe local reactions? Is there any data that they might be more predictive?

DR. ZELDIN: Not that we have seen across our experience. It is, as Dr. Weber says, a lack of association between the large locals and going on to something. No, we have not seen that.

DR. NELSON: Dr. Kelso I think had a comment on the asthma statement earlier.

DR. KELSO: I think you have addressed it as best you can, but I do not think we can confidently say that there is not an issue here with asthma because the formal study specifically excluded anybody who was on a controller medicine. We do not have formally performed studies done on patients who have persistent asthma. There is just no data there. And then looking at it after the fact in the

post-marketing data is important and that is really all the data we have about how the effect on asthma or the likelihood of a patient with asthma having a systemic reaction or having asthma as part of a systemic reaction, some of which there is clearly descriptions of in these case descriptions, whatever category they are under. The people took the pill and then they started wheezing. But I think we have as much data on that as we are going to get.

That might be something specifically to consider in terms of our thoughts about additional studies post-approval is to continue to assess asthma particularly if this is being given to people who have asthma.

DR. DAVIS: I also wanted to ask for clarification about the background material four-month pre-seasonal pooled efficacy analysis shows that patients with asthma, the confidence interval actually passes zero. Was there any sense that patients with asthma would not have as much effectiveness of this therapy?

DR. ZELDIN: Thank you for the question. Can I see the slide that spoke to our subpopulations from my initial presentation? The question is really I think of statistics rather than clinical question, but I would like to answer it for you. The question is essentially that in the patients with asthma, the question is the confidence interval crosses zero in the patients with asthma. Is that

an issue? When we look at the effect sizes, we think that the effect sizes -- relative LS mean difference. I think you can appreciate that these numbers are really quite consistent with each other. We believe that this issue is really one much more of sample size because that is the smallest population and not one of actual efficacy.

DR. NELSON: Since you have subpopulations up, on page 105 of the documents provided earlier, the issue of pregnancy was discussed. I know that they were specifically excluded from the studies here. But there is a statement in here that says in light of limited data regarding safety of ORALAIR during pregnancy, ORALAIR should be used during pregnancy only if clearly needed. The way of background for the audience, of course, we are aware that with subcutaneous immunotherapy, there is a recommendation to allow continued use -- the dose before pregnancy or perhaps at a reduced dose. I am wondering if you would care to comment on use in pregnancy.

DR. ZELDIN: The data driven answer is that for the women who became pregnant during trials, they were discontinued from the study and were asked to stop therapy. From a data driven answer, I do not have experience with respect to the pregnant woman and the outcome of the pregnancies. It would be a stretch to say anything more than that.

DR. NELSON: Would it be fair to say that if it were approved and recommended that we would recommend discontinuation upon becoming pregnant?

DR. ZELDIN: I think that the decision would have to be made between the physician and his or her patient. But I think without data, it is very hard to provide you with anything else.

DR. NELSON: Additional questions from the group.

DR. CASTELLS: Going back to -- if you had a woman who became pregnant during the study, would you be able to retrieve the data of what happened? Because I think that a lot of medications that we use nowadays during pregnancy were from women who became pregnant during the studies and not intentionally and then the data was analyzed. It would be extremely helpful. It is very expensive to do a study on pregnant women. What about retrieving the data of the woman who actually became pregnant? Would that be possible?

DR. ZELDIN: We could do our best to do that. You mean from a post-marketing experience to almost create something where we could try to answer that question definitely.

DR. CASTELLS: As Dr. Nelson said, we are making a recombination based on no data whatsoever so that would be a little data.

DR. WEBER: Different question. Returning to the issue of the two-month trial, which was a failure, but I believe there was another segment as a subgroup in one of the other studies where the two-month trial was effective. Do you suspect that this is a beta error, not enough data? Will you pursue that two-month treatment trial again or is this just an issue that is dead in the water as far as you are concerned?

DR. ZELDIN: At this point as I have said, we have looked at this study exhaustively. The study was appropriately powered. It was appropriately conducted. We used good centers. The patients were similar in all of the parameters as in our other studies. We take the data as they are and we think we are providing an appropriate approach and seeking approval for the four-month pre and co-seasonal because that is the one where we have consistency of effect. We have had some internal discussion about next steps, but we do not have a position yet as to whether to continue to explore alternative regimens.

DR. WEBER: You are fairly confident that you have enough data that you are really not dealing with a beta error that the group was not large enough.

DR. ZELDIN: The things that came to us we have looked at quite rigorously. From the sample size

standpoint, it was certainly right there. And the data as you saw are truly not compelling. We have to either find another reason or think about it a little bit further.

DR. SAPER: I have a few short questions. Again, looking at risk with immunotherapy, it is variably recommended that you not have vigorous exercise within X amount of time after having immunotherapy injectable. Is there any risk associated or any advice that you had given to participants regarding timing of exercise? Another would be history of anaphylaxis. Was that also an exclusion? I forget if that was in our materials. And anything specific on food allergy if it did not relate to anaphylaxis. And then of course on anaphylaxis, for exclusions, how did you define anaphylaxis because we had some issues with the definition here? How would that have been defined as exclusion?

And then the last one is how did you define pollen exposure. When you see high pollen exposure, we have noted tighter data. Pollen exposure is not only related to nature's release of pollen, but lifestyle of the individuals. If you have a bunch of soccer players, they are going to have a higher exposure. If you have people in the office, they are going to have less. That is my list.

DR. ZELDIN: Let me try to take them in order. With respect to exercise, we did not provide to patients in

the clinical development program guidance to limit exercise. They had no limitations in what they could do and how they could proceed.

With respect to anaphylaxis and food allergy, those patients were not excluded from participation or enrollment in our clinical development program. We did not systematically exclude them.

With respect to pollen exposure, the definition of pollen exposure of course is based on where the pollen trap is located. It is a site-based definition. It was not and it would be wonderful at some point to be able to do this in our clinical trial to be so granular as to be able to have it on a patient-by-patient basis. But the way we cut it into high, medium, and low was based on pollen counts at the site for each of the sites. We simply cut it in thirds. We do not have the granularity with respect to a patient-by-patient basis. Unfortunately, we do not have specifics as to whether a patient was more or less likely to have spent more time outdoors or indoors. We just do not have that level of granularity.

DR. SAPER: You had no occupation or lifestyle questions at enrollment.

DR. ZELDIN: I just do not have that answer.

DR. RIEDL: Two questions that will help me in good conscience answer the safety question that was posed.

One is that as I understand it, you are proposing that this would be used in the dose escalation format. Starting with an observed 100 dose and then going up. Is it 200 and then 300?

PARTICIPANT: Yes.

DR. RIEDL: Maybe you could comment on why you are sticking with that. The reason for the question is as we have heard before, the day one reactions have been to the 100 dose. At least I have not read or heard anything that indicated that you saw reactions with any frequency with the second or third day, at least more frequency than the late reactions. I guess my question is what is the purpose of the dose escalation? If you are escalating the dose for safety reasons, why would you not have those be observed as well?

DR. ZELDIN: Let me try to answer that. The first point I believe you made and I just make sure we are aligned together. Indeed, we are proposing a dose escalation regimen for approval. That is the regimen that we studied in children. That is the regimen that we studied in our European study, the VO34.04, the first study that you saw. In those studies, we saw no serious drug-related adverse events. No study in our clinical development program did 100 IR elicit a serious drug related treatment emergent adverse event.

I shared with you in our VO53 study, a long-term study. That was a direct administration study. By direct administration, I mean that from the first day the patient took 300 IR. It was in that study that two patients experienced serious drug-related treatment emergent adverse events on the first day and within minutes of dosing. It was the 300 IR dose that prompted those responses.

I think an important feature and why we are suggesting that we move forward with the dose escalation is because it was the regimen that we looked at in children and because it was the regimen that we looked at in our post-authorization safety studies and it is the regimen for which we have five years of experience with over 112,000 patients treated. That is the essence of it.

DR. RIEDL: That is helpful. The background on that is when we do drug challenges in our offices and Dr. Castells is the world expert on this so she can correct me. But generally speaking, if we are going to escalate the dose, we like to do that under direct observation. While I understand that is helpful information, that is your experience, it is a little bit at odds with what we would do at least in my current clinical practice. If we are escalating a dose that we anticipate could cause an allergic reaction, we like to do that under observation. In this case, the approval would send people out escalating

the dose with theoretically at least it sounds like a risk that they would cause a reaction.

DR. ZELDIN: You asked a very good question though. You said have you seen anything on those subsequent days. We have seen two important things. One is that when we go to this dose escalation, the rate of adverse events is substantially lower than when we start off down with 300 IR and those second and third days have not been days where we have seen -- we saw no such events in the clinical development program and the post-authorization safety study. I believe among the 112,000 patients treated, we had one laryngopharyngeal event in a patient on day three of 112,000 patients treated. We feel that this is the appropriate regimen as it has been ex-US. We think it is also the appropriate way to go and it is frankly the conservative way to go in the US as well.

DR. RIEDL: That is helpful. If I can just throw in my second question quickly. I ask this honestly out of -- I am just not educated on how this works. The amount of experience you have with this in other parts of the world is impressive. Can you comment on how this has been implemented in Europe, for instance? And my question specifically relates to the fact that I think all of the safety factors, the patient selection, and the ability to recognize and treat allergic reaction, the ability to

educate patients on this are heavily centered on this being prescribed in my opinion by specialists who are experts in this. I could be wrong about that, but that is my view of the world.

Could you comment on who is in charge of this therapy in other parts of the world where your safety data does look reassuring?

Dr. ZELDIN: Our experience ex-US and we would expect our experience in the US as well to be with physicians who are well trained and experienced in managing allergic diseases and the potential consequences of those treatments. That is exactly the population of physicians who have engaged in Europe and the ones that we would like to engage here in the US. Exactly that. Thank you.

DR. PETERSON: I had a question dealing with the mitigation of adverse reactions and basically from the patient population. Itchy mouth, sore throat. What will you say to them that keep patients coming versus I am out of here. I do not want my child or me to have that. Do you have a series of steps that people can take for themselves or refer to somebody? How does that work?

DR. ZELDIN: I would love for Dr. Golden to speak to that because as a clinician who will face this type of question, I think he would really provide some insight.

DR. GOLDEN: Thank you very much. That is a

great question. It borders on a whole lot of other questions as well. It is not dissimilar in some ways from the patient on subcutaneous immunotherapy that is alarmed by this large swelling. I am generally going to reassure them and say that is expected. It is not a predictor of severe reactions. It usually, but does not always get better with continued treatments. It is not a reason to give up on the treatment. Everything I just said probably applies to the itchy mouth, itchy throat. 99.9 percent of those patients in these trials did not develop serious or severe adverse events. It should not be an impediment. It is expected. Over half the patients develop those symptoms. I think it is very analogous to the large local reactions. I feel comfortable providing that kind of reassurance.

I am always going to counsel the patients and parents that I want to know if there is anything worse or different, if they feel bad in other ways. There is an important need for careful monitoring and surveillance. There is a reasonable way I think to counsel those patients and to keep them involved and comfortable with their treatment.

There were other questions about risk factors though that maybe I should come right back to because it is part and parcel of this. We are counseling our patients.

Again, in subcutaneous immunotherapy, there is a recognition of a number of risk factors, but they are not exclusions. There is clinical judgment. As allergists, we are experts in making those judgments based on published trials and clinical evidence. If a patient has food allergy or prior history of anaphylaxis or asthma, those are concerns. This is where the physician has to assess the individual patient, have a discussion with the patient and determine whether the risks are reasonable and acceptable or whether maybe this patient should be counseled otherwise. But I do not view them as exclusions necessarily. This is all part of the counseling and clinical decision making when we make the initial judgment. Are we going to suggest to begin immunotherapy for this patient?

DR. CASTELLS: I wanted to go back to Dr. Riedl's comment and two points about those comments. First of all, we have created guidelines for challenges and desensitization. It appears to me that the 100 units do not seem to trigger any reactions then. 200 and 300 might. I would call it a mini-desensitization. In three days, you get to 300 or something like that.

Essentially, the standard of care for doing this would be in an allergy place, in a place where we can control that. Sending the patients after the 100 in the

office and sending them home would not conform to my standards and the ones that I define in the guidelines as the standards of challenges or desensitization. Essentially, what I would do with your dose would be 50, 100 and 150 in one day as we do for hymenoptera in an office and that is how it will be up to 300, not sending the patient home. Because I am actually concerned about that and the fact that the patient may be home, may forget, may take the 200 three days later or four days later the other doses. A small effect of desensitization that you want to achieve. And to achieve that, you would be best to do it in a very safe environment in a way that we could actually monitor that very closely.

And the second point is as you were mentioning, people who are experts on allergic diseases or treating allergic diseases, I think we need to emphasize that in terms of a pill is a pill. It could be delivered by a primary care physician. We have to be really cognizant about that possibility and what the risks of that might entail.

DR. ZELDIN: We certainly agree. I think the only comment that I would make on your first point is that we are data driven and we have experience now both in our clinical development program, in our post-authorization safety studies, 1500 patients treated in one, 1700 in the

two post-authorization studies and over 112,000 treated in the real world setting that suggests that the regime that we have approved is quite a reasonable one with a favorable safety profile. That is the regimen with which we have experience and that is the regimen that I can speak to comfortably here and say this is what our data have shown in five years of post-marketing experience and 20 million doses and 112,000 plus patients including 37,000 children. That is what I know.

DR. APTER: I appreciate your experience. Given that you are asking some people including children probably to take pills for six months in which their mouth itches and their throat hurts and they might not find it helpful, I think they are likely to stop at times and then restart. There has been at least one paper from the Netherlands where adherence to sublingual and also subcutaneous immunotherapy was not great. Are you going to make recommendations about what clinicians should do to restart medication if patients lapse for a while?

DR. ZELDIN: Our preference to be conservative is that if there has been an interruption for greater than seven days that that patient be seen back in the physician's office and take that first dose under observation. We think that is important. Again, it is conservative, but we think it is important. We would

rather err on that side. Are there enormous data, Dr. Apter, on that point? No. It is just a clinical judgment.

DR. NELSON: On the topic of restarting, I would like to revisit the question I posed earlier about what might be contraindications to resuming therapy either immediately or after a break in therapy?

DR. ZELDIN: I think your question touched on re-challenge. We do not have experience on re-challenge. Our advice to the patient, to the clinician in our proposed prescribing information is that the rare patient who should have such an event should not restart therapy without consulting with their physician. I think, as you said, with pregnancy, again, we would want to err on the side of conservative. These events are rare should they occur. Maybe this is not the patient who should continue. But again, that is the most conservative approach. It is not a data-driven approach because we have not formally re-challenged these patients.

DR. NELSON: To restate, we are talking about pregnancies, systemic reactions, and anaphylaxis. Is that a fair statement?

DR. ZELDIN: I think that it should be the physician's judgment with their patient. I cannot put that on to a doc or patient. But I think that it is appropriate for the physician and their patient to have that discussion

before restarting or continuing therapy. In essence, that is what I would suggest.

DR. SAPER: In other sublingual immunotherapy trials and reports, the oral pruritus tends to resolve quite quickly like within a few days or a week. I am not hearing that from you at this dosage. Do you expect that the patients that are in active medication will continue to have undesirable oral symptoms?

DR. ZELDIN: The overwhelming majority do not. The symptoms resolve shortly thereafter after starting therapy and they do so generally without treatment and do not recur.

DR. SAPER: And that is within the days to awake -- three to seven days and it is gone.

DR. ZELDIN: That is a predominance of our experience.

DR. SAPER: And then back to safety issue. If that does not go away, I think Dr. Weber was asking. If that continues longer, is there a higher risk associated?

DR. ZELDIN: Our experience is that if that occurs longer, that is not associated with any increase risk of an adverse event. There are the occasional or the rare patient who have continued local symptoms and who play through without any worsening or furthering of those symptoms.

DR. SAPER: Would it be fair to assume that among those patients that continue to have oral symptoms, those represent a higher dropout group?

DR. ZELDIN: It is actually not the case. Not necessarily the case. Some folks do not like it from the first days and stop. They just do not like the tingle. It can be the same level or gradation. For them, it is well worth the relief that is provided by the efficacy of the product. It is very patient dependent.

DR. LIERL: I am just curious about -- I guess if you knew this, it would be from your post-marketing surveillance. What is actually being done in Europe as far as cycling patients sort of on and off of this treatment? For example, if they take the tablets for two years, they feel better. They stop and then maybe after a certain number of years, they start to have symptoms again and go back on it. Do you have any sense of that going on?

DR. ZELDIN: The product was first approved in Germany of 2008. The typical regimen would be three years of discontinuous treatment. You start four month pre and co-seasonal. You finish that year. You have a several-month hiatus and then you pick it up again the next season for three seasons. We do not have specific experience who are interested in gathering that over the coming years with patients who perhaps as you say feel great after one year

or two and maybe take a break or what happens in real-life settings for patients who complete three years of treatment. What is the real-life experience with respect to sustained effect? Those were questions that were actively interested in and considering in and working to design efforts to answer those very questions. It is exactly right.

I cannot tell you today that we have a body of substantive data that I can share with you.

DR. KELSO: If we lump together since these are really rare events, anything that has been labeled as anaphylaxis or anything that has been labeled as a serious laryngopharyngeal, whatever that category was, whether it occurred during all the studies themselves or post-marketing, if we lump all those together, how many are there? What is our numerator?

DR. ZELDIN: It is not a tough question. I am just trying to process. I am doing the math quickly in my head. I am going to make an assumption that if the doc said it was not treatment related -- if we had one episode, Dr. Kelso, where it seemed that it was clearly a food reaction to food. If we cast those aside, I think we can say that there were between all comers and I am thinking quickly, I think we have across the development program, post-authorization safety studies and in the 112,000

patients, I think it is 25.

DR. KELSO: Including anaphylaxis and serious -- how many of those occurred on day one when the patient took 100 IR tablet?

DR. ZELDIN: A substantial majority.

DR. KELSO: On day one when they took the 100 IR.

DR. ZELDIN: Other than two in the clinical development program, which occurred on day one, but with 300 IR, a balance generally occurred on the first day and it would have been with 100 IR. It is a back of the envelope thing. I do not want to be wrong. It is certainly the majority.

DR. KELSO: That occurred on the first day with the 100 IR.

DR. ZELDIN: Yes. That is absolutely the case.

DR. KELSO: Smaller numbers like on day two when they took the 200 at home and on day three --

DR. ZELDIN: There was none. There was none on day two across the entire program in all these 112,000 patients treated. There was one severe laryngopharyngeal reaction that was reported on day three in 112,000 patients and then a handful scattered subsequently.

DR. KELSO: On four plus days. What is the rough range of what that four plus days is?

DR. ZELDIN: Maybe Dr. Bons can speak to it. But

I believe it was out -- the furthest one was maybe out two months. Is that correct? The last severe laryngopharyngeal reaction? We go out to day 21. One was five months. Thank you, Dr. Bons. That five-month one was considered by the report to be not related. I think I will stand by my memory, which says I think two months was the latest, somewhere in that five, six, seven week.

DR. KELSO: Of these 25 events that we know of ever with the studies themselves in the post-marketing experience that most people around this table would all call them anaphylaxis of these roughly 25 events. Upwards somewhere in the high teens probably occurred on day one with 100 IR tablet and then like ones and twos and whatever for these other circumstances on day two, day three, day four plus. Is that correct? No day twos and only one day three and then a handful that could be out as far as who knows.

DR. ZELDIN: It sounds like some weeks.

DR. KELSO: But the bulk of them are on the first day.

DR. RIEDL: I am not trying to show anybody up here. I am looking at the SAE reports here. There are some day two. There is a day four. There is a day three. I am just reading out of the tables here. I just want to make sure we are all clear on the events that have

occurred.

DR. ZELDIN: What I am trying to address are the events that were considered either anaphylaxis or severe laryngopharyngeal reactions.

DR. RIEDL: I am just reading. I am looking at table 43. List of serious adverse events. There is a 32-year-old male, pharyngeal edema, swollen tongue, lip swelling, dyspnea, chest pain, renal pain, day three, 30 minutes after the dose.

DR. ZELDIN: I am sorry. I have not memorized the table numbers.

DR. RIEDL: I am just showing you what the data is. This is table 43 on page 114 of the briefing document.

DR. ZELDIN: This was a case in the post-authorization safety study. Do you want to speak its categorization? That would be helpful.

DR. BONS: You are referring to -- case, which was reported during the post-authorization safety study in adults in 2008, which is the case 2008 642.

DR. ZLEDIN: Correct.

DR. BONS: This occurred in day three. This 32-year-old male who developed progressively a swollen tongue, lip swelling, dyspnea, and pharyngeal edema. This case spontaneously resolved.

As you know in post-marketing setting, it is a

lot of information and often missing. We have developed a methodology to address what we call severe laryngopharyngeal reaction. There was severe laryngopharyngeal reaction that is described in the briefing document, Associate Respiratory Symptoms and Treatment. In this case, the symptoms were not severe laryngopharyngeal reaction.

DR. RIEDL: I understand that. I can see that in the table. Again, I do not want to get into an adversarial relationship here, but I just want to -- what I heard you say is that none of these events happened on day three and that is actually not what I see on the tables.

There is actually another case in table 41, which is a 55-year-old gentleman on day three who had dyspnea, cough, throat irritation, oral discomfort who actually got steroids and Salbutamol administered.

Again, I just want to be clear. What I heard you say to Dr. Kelso was that none of these events happened on day three. I do not believe your data actually -- that is what it shows.

DR. BONS: I would like to clarify. If I may display the synthesis for adults and for children, thereafter on the time to onset on each type of adverse event of special interests, which are the QS111 and maybe something like that. No, the synthesis.

First of all, the evidence(?). We have had eight cases possibly consistent with anaphylaxis. Six occurred on day one, two occurred after 30 days. These two cases were not considered to be related to ORALAIR by the report. This is for the adults and anaphylaxis. Regarding the adults and severe laryngopharyngeal reactions, we had received nine cases. Five occurred on day one within minutes of the first dose, which was 100 IR. One occurred on day three. That is the one we have just discussed right now. And three occurred after day three.

Regarding the children, we have had four cases possibly consistent with anaphylaxis, two occurred on day one and two occurred on -- one on day seven and one day 45. Regarding the children and adolescents, we had received five cases consistent with severe laryngopharyngeal reactions, three occurred on day one, one occurred on day four, but was not considered to be related with the treatment by the reporting physician. And one occurred on day nine. All resolved.

What we say is that the vast majority that occurred on day one, but were realized that some reactions are delayed. This is why we strongly suggest to implement a immediate plan, pharma(?) plan describing all the signs and symptoms.

What you can say from our post-marketing

experience when we look at the case with the countries where they are reported that the patients they recognize very easily particularly the oral pharyngeal symptoms because they describe very clearly either sensation of swelling difficulty, sensation of foreign body. It is very clearly defined. We will explain to them in the packet information leaflet all the symptoms, which are described by the patients themselves.

DR. NELSON: I believe Dr. Kelso may have a comment.

DR. KELSO: No, that answered my question. I actually think that is very helpful and I think that is accurate. My assessment of this is these clearly are serious potentially life threatening events. They seem to be exceedingly rare. I think it is accurate to say that the majority of them do in fact occur on day one. We can discuss, I assume we will, various ways to address this risk. One appropriate way to moderate this risk it seems to be just what the sponsor has recommended, which is that the first dose be given under observation in a physician's office. That kind of covers the bulk of them that happen on day one.

The others could happen any time. They are exceedingly rare. It could happen any time and there are various ways to moderate that risk, one of which could be

to recommend or require that patients have self-injectable epinephrine, which I would actually advocate for not only for that reason that it is exceedingly rare, but potentially life-threatening event that could happen at any time. But that also there is this issue about the asthma, which remains inadequately studied. We think of asthma as a risk factor. Two-thirds of all anaphylactic deaths happen in patients who had pre-existing asthma. Now, we do not have enough data here. We do not know the answer. But given the lack of study about that question, which would be another reason in my mind for us to consider saying that patient should have to have self-injectable epinephrine available if they are getting this treatment.

I think the way that it has been described seems accurate. I think since we have all been picking apart the laryngopharyngeal -- I think it is fair to just lump them all together, talk about what is the total number we are talking about. It seems quite small. Most of them really are on the first day and then to discuss other ways other than having the first dose given under observation, other ways that we might moderate this small, but serious risk.

DR. APTER: Another precipitant of one of these reactions occurring, we do not know when. It could be a lapse in therapy preceding this.

DR. NELSON: I will ask one final question before

we move into the voting phase and that is during the description of the meaningfulness that was described in the pre-meeting materials that were provided, very appropriately you refer to the effect size. It was reviewed both by the FDA and your company today regarding a decent effect size that was indeed comparable to drugs and pharmaceuticals as well as subcutaneous immunotherapy. I do not think there is much question in that area.

You also alluded to the fact that there is a preserved peak season effect when given over multiple years as well.

If we look at a disease state on the spectrum of no treatment, non-disease modifying treatment in the form of pharmacotherapy and then disease modifying treatment such as subcutaneous immunotherapy, where indeed does sublingual immunotherapy in this particular product fall given that the language has been relatively soft regarding whether this is indeed a disease-modifying drug.

DR. ZELDIN: I think our gestalt sense of the experience and obviously, Dr. Rubin and Dr. Slater have their sense of things. I think what we can say based on our experience in this long-term study is that our data are suggestive of a post-treatment effect. With all the things we discussed this morning and this afternoon, I think that is the appropriate place.

DR. APTER: One final question. Didn't you say that all the studies were in patients that were under 65?

DR. ZELDIN: In all of our studies, patients were under 65.

DR. APTER: I am wondering if we shouldn't say between five years of age and 65.

DR. ZELDIN: I just could not hear.

DR. APTER: I am sorry. I am worried that we should say for persons between 5 years and 65 years of age rather than 5 years and older.

DR. NELSON: We will take that as a comment. I am sure our colleagues at the FDA will as well.

DR. KELSO: I guess I have two procedural questions. I wonder if we should answer questions three and four before one and two. And then the other is where do we put things like -- Andrea just mentioned about -- among these four questions, is there an opportunity for us to say as I have suggested maybe requiring self-injectable epinephrine. As Andrea said, requiring an upper age limit. Among these four questions, where does that fit? Our suggested amendments to the possible approval.

DR. SLATER: Thank you for that question. As we move forward to discussion of the four questions, I would like to point out to you that even in the first two questions in which we ask the committee to vote yes or no,

we are deeply interested in what you are concerned about and what your recommendations are. Even for questions one and two, we feel strongly that we would like to hear your discussion. We have been scribbling furiously all day listening to what you are saying. We are very interested in how you react to the questions aside from your yes or no vote. All of these considerations are being carefully noted.

DR. NELSON: Throughout the entire proceedings. I think one way to address this will be to go through the question, ask if there are any burning comments that need to be made before the entire committee, conduct our vote, and then give the opportunity for members to provide any additional comments for capture afterwards. Sound like a reasonable plan for the committee?

DR. KRAUSE: Just to add though that if one of the members vote depends on some modification of the question or some additional thing, I would put that in the category of burning issues -- we really do want to hear about issues that might change one way or another.

DR. NELSON: First question. Do the available data support the efficacy of ORALAIR for the treatment of grass pollen induced allergic rhinitis or conjunctivitis in persons five years of age and older when administered prior to and during the grass pollen season? Are there any

interpretation type questions or comments at this time?

DR. SAPER: I agree with Dr. Apter. Can we change that of instead of and older to say five years of age through age 65?

DR. KRAUSE: I think we would not change the question at this point because the sponsor has come in and is requesting an indication for age five years and older. But if you have reservations about voting in favor of five years and older, you can say you would vote yes if it were 5 to 65, but you would vote no if it were five and older if the level of your reservation reaches that level.

DR. DAVIS: I have a similar concern about there being -- it says administered prior to and during. I would want there to say at least four months prior to rather than two months prior to. That would be something that would potentially change the vote.

DR. SLATER: The sponsor clearly has asked for a four-month prior to grass pollen season regimen. That is part of their request. I think you have not only seen that in their briefing document, but you have also sensed it in their presentation today regarding the two-month protocol. I think that is pretty clear in the way the question is asked.

DR. NELSON: Additional comments or questions?

DR. PETERSON: I just want to make sure that the

medication would be taken as we have discussed it that it would be every day people would take it and for the prescribed amount of time that it is taken. I have some reservations or questions about real people being able to follow through in that kind of regime. I am a little concerned about the stop/start especially when it is during the season that you do not have your allergies.

DR. NELSON: Noted. Any comments?

DR. SLATER: It is a legitimate concern. I think it would be a concern with many daily medications that they be taken as instructed. If you have particular concerns about starting and stopping this medication as opposed to others, I think that is something that we are eager to hear about. I am not sure how we incorporate that into this discussion. But I think what we have been hearing is that you would like some instructions to practitioners and to patients as to how to handle interruptions in therapy. I think that is a valid statement.

DR. PETERSON: That would help. Since you do not have a group that started and stopped and "misbehaved" during that, we do not have anything to look at data wise.

DR. KRAUSE: Is your concern more from the efficacy or from the safety side? If it is more from the safety side, of course, everybody is stopping and they are restarting the subsequent year at least.

DR. PETERSON: It is a little bit of both. If we say that this will help you and we know that if you stop and start, it won't. Then it is the ethics side. It is not right. And according to the newspaper, it is a pretty expensive drug as it turns out when they get to buy it. From the safety side, I am very concerned that if it does harm to somebody, that is not acceptable. If they stop and start and when they start again it is less effective, at least it is not harming them. I would hate to have somebody in jeopardy. I do not know. If you are building up immunity and I am not sure that that is what this does, anaphylaxis is more prevalent once you start and stop and start again. That would be of concern too.

DR. APTER: Are there any recommendations on the second year when they start? Should the second year I am wondering be also started under observation?

DR. ZELDIN: That is our recommendation that each year they come back to the physician's office and restart under observation --

DR. NELSON: For those unable to hear, the sponsor has indicated that they do recommend a restart under an observed therapy during the second year.

DR. KELSO: That was my question.

DR. NELSON: At this time we will move to a vote on question one. Before you are yes on the left under the

plus sign, no on the right under the negative sign, and zero for abstain. Your opportunity to vote in confidence is before you and you can vote no. If you were uncomfortable with the question as written, I would recommend voting no and making sure that we lodge your reservations regarding how it is specifically written. We will capture that as one of the post vote comments.

Perhaps while that is coming up, the committee would like to add any specific notes or comments that go with respect to efficacy of ORALAIR going forward that have not been made already.

MR. JEHN: We have the official vote. For the record, I will read the votes. Dr. Apter is a no. Dr. Davis, yes. Dr. Kelso, yes. Dr. Nelson, yes. Dr. Riedl, yes. Dr. Castells, yes. Dr. Weber, yes. Dr. Saper, yes. Dr. Peterson, yes. And Dr. Lierl, yes. Again, one no and nine yeses.

DR. SLATER: Dr. Nelson, if I may. I just want to state clearly that it sounds to me like if the indication had been for 5 to 65 years of age, this vote would have been ten to nothing.

DR. NELSON: I would accept that as being true.

DR. SLATER: Is that an accurate statement?

DR. APTER: Yes.

DR. NELSON: Question number two. Are the

available data adequate to support the safety of ORALAIR when administered to persons five years of age and older? In your deliberations, please consider the available safety data for children and adolescents 5 to 17, adults 18 to 65 years of age and elderly greater than 65 years of age. Clarifying questions or comments at this time from the committee.

DR. SAPER: -- presented no data over 65. We also cannot amend this question, correct?

DR. APTER: Is there post-marketing data over 65?

DR. ZELDIN: I hate to be in the middle of a vote. Frankly, the issue of 65, we freely acknowledge that we have not studied patients over 65 years of age. I can speak I believe on behalf of the company. We are quite comfortable at this stage saying 5 to 65 years of age without hesitation. It is just not an issue for us. I understand why the question was asked this way and I am perfectly comfortable with that. But if you are giving me the opportunity to speak on behalf of the company then I can certainly say that definitely. If the language is changed to 5 to 65, we will be perfectly at ease.

DR. NELSON: Dr. Kelso.

DR. KELSO: Again, you have said all this information has been captured. This is where my question about the self-injectable epinephrine comes up. I guess I

am not sure how to answer the question relative to the fact that I feel that if it is approved that there should be a requirement that patients who are on this therapy have self-injectable epinephrine available to them. Does that change my answer to this? Does that make me a no?

DR. NELSON: Dr. Slater, I was going to bring this up if he did not, which is our interpretation with respect to this. Can we assume that epinephrine is not being required as part of this question?

DR. SLATER: I think we are asking for a statement from the committee as to the committee's sense of the safety of the product. All products even those that have serious adverse events can be used in a context that maximizes their safety and that fails to maximize their safety. Sometimes that has to do with the package instructions and sometimes that has to do with real-world use. I do not think we can control all of those. What we are asking the committee is to develop a vote on the safety of ORALAIR when used as described in the materials provided by the sponsor.

We recognize that there are aspects to this that worry members of the committee and that has come across loud and clear. We are happy to hear these concerns.

We are specifically leading you in a certain direction by asking you to comment on the available safety

data for each age group and we want to hear -- we have already heard a discussion about the over 65 that I think is over.

But I do not think we want to qualify the question so much that it becomes difficult and almost meaningless. We have ahead of us discussions with Stallergenes that are going to be ongoing and we are going to take into consideration everything you have to say. For the moment, I would like to leave the question as it stands and see how the committee treats the question.

DR. CASTELLS: I appreciate that. I just wanted to voice again that I am not sure that we are protecting the asthmatic population. I am just wanting to voice that concern. That emanates with my experience with food allergy and the fact that all those kids who died were asthmatic, mild intermittent asthmatics. Whether we have enough data, what has been provided, or we are looking at the reality and like the field. I feel slightly uncomfortable in that.

Going back to Dr. Kelso's, if we are not protecting them, should the protection be made by providing an EpiPen. Those are my two concerns.

DR. DAVIS: I have a concern with the fact that about 15 percent of children have mouth edema and they have a smaller airway. I do have a concern that the currently

provided information as a means of pharmacovigilance does not include all of the information that I feel that it should include in order to really warn patients of the potential serious adverse events.

DR. KRAUSE: Just to add a little bit to what Dr. Slater said earlier and that is if there is -- I heard the comment about the EpiPen from two of the members of the committee. If there were a lot of the members of the committee who feel that way, it would be good to hear that from a lot of members because that gives us a sense of the depth of feeling on that issue as compared. Even if it is not part of the vote as has been said, the individual comments are very important to us.

DR. SAPER: Just a little clarification on what you said, Dr. Slater, about -- this is basically our overall feeling as to whether this medication that is being considered is safe. However, you will take into account our hesitations and those are in a sense separate from our answer to this question. On that, I have specific concerns about the length of time of dissolution for this particular tablet and the concern of the GI signal that has not been adequately addressed that I could see, a small percentage of people, but it may be a significant signal going forward and any risks associated with swallowing the tablet rather than having it under the tongue. I say that asking the

question because that is separate from my feeling of the overall safety in the vast majority of people. Are we asked to essentially blank it for the vast majority of people and then just assume that you will take care of the safety concerns that we have raised here?

DR. APTER: I just want to ditto the concern about the need for the EpiPen especially in some patients and especially in patients who might have asthma. Although I also understand the overall safety of the medication.

DR. DAVIS: I want to also ditto what has been said about the epinephrine pen.

DR. RIEDL: And I would add my supportive comment to the EpiPen issue as well. My concern really is that while these are clearly rare events, there is no doubt, they are quite rare, they are serious and they are predictable in some ways and they are life threatening. I am very impressed with some of these descriptions. This is real life threatening anaphylaxis that happens. Again, it is foreseeable though it is rare.

My concern really is that once if this drug is approved that that risk is communicated clearly and upfront to both physicians and patients because the reality is once this is out there, anyone can prescribe this, which is fine. But I really do strongly believe that the physicians prescribing this need to have good judgment in patient

selection and in managing these risks. I think one of the ways to communicate that is to say that you should have epinephrine available to the patient to treat this. This is a loud and clear message that says this is a rare, but real risk. If practitioners are comfortable with managing that risk, then by all means this looks like it is something maybe beneficial. This is one way to get that message across in a very clear fashion.

DR. WEBER: I am wondering if somebody can reinforce for me whether our practice parameters spell out the requirement for EpiPen for subcutaneous immunotherapy and how that it is worded. Off the top of my head, I do not recall. I would like to know. I think we are dealing with the same situation here.

DR. SAPER: I think the seminal difference though is that this home therapy. When you do subcutaneous immunotherapy, you are in the office and you are being monitored. I think those concerns separate out on that.

DR. NELSON: I believe the practice parameters now refer to an absolute requirement. I am sure I speak on behalf of the committee members. When we refer to EpiPen, we are really talking about injectable epinephrine and no favoritism on products. People will chime in if that is the case. I am sure I slipped in that area myself.

I will give one comment before we move to vote as

well and it will be reflected in the way that I vote. The data for me looking at the stratification by age was very useful. For my count, I only saw about 65 subjects age five to eight that were included in these studies. It is difficult for me to draw conclusions on that population with an N of that size.

DR. PETERSON: Just to weigh in, not that any of the others have not already said it. I think a study or something with more of the asthmatic patients taken into account. The EpiPen, yes. Airway obstruction. Although it might be rare is very life threatening. A lot of the patients with other diseases might already be familiar with that. There is no information on the elderly and you can choose to enter it or take it out of here. The time it takes for a tablet to dissolve in a five-year-old's mouth is of concern. I just do not see them wiggling around. Just how that works. Because I am interested in kids, more on younger children between five and nine or such.

DR. NELSON: With that, I think we will move into a vote on this question. If the team is ready, we will go ahead and vote now.

DR. RIEDL: I apologize. Can I just ask for clarification because Dr. Slater mentioned that the sponsor had come forward with some proposal? I just want to be clear. They are not proposing as part of their approval

process that there would be a requirement for self-injectable epinephrine. These may be labeled negotiations. I understand that. I just want to be clear. You had mentioned that the sponsor has put forth some indication of how this would be used.

DR. SLATER: No. If I said that, I misspoke.

DR. SAPER: Could you clarify one last time what a yes vote means to you from this group and what a no vote would mean?

DR. SLATER: Let’s accept at a preamble that is not on the screen in front of you that there is no drug or biologic that is completely safe. That there are risks associated with all of them. Safety is defined here as safe in the context of the benefit that is a reasonable safety that in the context of the benefit to be expected. If you are unhappy with the safety data that you have, we would like you to tell us that either with what you say or how you vote. If you are satisfied that the data are adequate to support the safety when administered in individuals five years of age and older then we would encourage you to have a yes vote. All of the other qualifications about that we will take into very serious consideration.

DR. SAPER: Thank you.

MR. JEHN: Let’s go ahead and vote as before.

This is the vote as tallied. Dr. Apter is a yes. Dr. Davis was a no. Dr. Kelso was a yes. Dr. Nelson was a no. Dr. Riedl abstained. Dr. Castells was a no. Dr. Weber, yes. Dr. Saper, yes. Dr. Peterson, yes. And Dr. Lierl, no. We have five yeses, four no's and one abstention for the vote on question number two.

DR. SLATER: Dr. Nelson, may I ask a question? If you do not mind, could each of the four no votes articulate for us the reason or reasons that they said no.

DR. CASTELLS: I am happy to do that. I do not think we have enough data to say that we are protecting the asthmatic population and that the requirement for an EpiPen is not made.

DR. DAVIS: The reason why I said no was because I did not feel that the safety data in ages 5 through 17 and mainly that younger age was adequate enough to say that this was safe in that population. I think that injectable epinephrine should be given or required of these patients. And also, the fact that the elderly patients greater than 65 were not assessed.

DR. NELSON: In general, I agree with the colleagues who voted yes regarding the general safety of the product, but specifically that very young age group I just think there is not a lot of data. Had we eliminated the age stratification, I would have voted yes.

DR. APTER: Can I say why I would have voted no? I voted yes, but I would have voted -- I thought that the EpiPen still would have been taken under consideration and we already settled the matter about 65 so I voted yes. I am unison with everybody.

DR. LIERL: I am also concerned about the injectable epinephrine issue and I just think it should be a stipulation of approval especially since this in our country, I think this is going to go viral and will be prescribed by a lot of non-allergists primary care doctors probably that may not prepare the patients for the possible adverse effects.

I am also just still concerned that the starting dose is too high. Since most of the serious adverse reactions and the potentially life threatening adverse reactions happen on that first dose. It is like if you are doing subcutaneous immunotherapy and you start with your maintenance file. We do not do that. Why don't we do that? Because patients would have systemic allergic reactions. I just still think that consideration should be given to backing the dose down by a ten-fold dilution or even 100-fold dilution and take some of those four months to build it up. It might be much safer. Those are my two major concerns.

Also, I agree with the questions that have been

raised about safety for patients with persistent asthma and the possible triggering or exacerbation of eosinophilic esophagitis. I guess we will discuss them under future studies.

DR. SLATER: May I have 30 seconds with my team? Thank you.

DR. NELSON: The referee is back from the replay booth.

DR. SLATER: At the risk of making a long day even longer, I do apologize for this. First of all, I think Dr. Riedl abstained and I failed to ask you why you abstained. I am sorry.

DR. RIEDL: I will be honest. I did not like the question. I think there were so many caveats that we had to -- the data is the data. It is not necessarily the sponsor's fault. I just thought the question was far too simplistic for me to give a valid answer one way or another. It was due to all the factors that have been raised.

DR. SLATER: With your permission, I would like to pose another question for the committee to answer.

DR. KRAUSE: To give you a preview of what Jay is going to be writing so you can be starting to think about it, the idea would be to ask you to vote on a question that stipulates some of the things that gave rise to concerns.

Stipulating that epinephrine would be made available to people, stipulating that subjects over age 65 would be excluded that we would be talking about that is the upper limit and having heard some concern about the pediatric population stipulating a lower end on that as well, which might then allay some of the concerns about the pediatric population. I think it would be helpful to us to see whether making those kinds of changes to the question would dramatically change the outcome of the vote.

DR. PETERSON: You are talking about raising the lower end from five raising it up or what?

DR. KRAUSE: Yes. We will see how he writes it.

DR. NELSON: It looks like they are recommending a lower age of 12. Is the committee comfortable with that or they would like to push it down even lower?

DR. KELSO: You had specifically commented that the lack of data not really a safety signal, just a small end for the very young children and the group that you had commented on I think you said five to eight was where we were missing. I guess I would be more comfortable with nine.

DR. NELSON: Two separate votes for A and B is what we are looking at. Let’s try again. Are the available data adequate to support the safety of ORALAIR when administered to persons five through nine years of

age? We will vote on that question singularly at present unless there are any other questions or comments. Age five through nine.

DR. KRAUSE: If someone on the committee had a comment that the cutoff of nine versus ten is one that gave them a huge headache and a year or two in either direction would make a different that might still be useful to hear, but otherwise it would be good to go ahead and vote on this.

MR. JEHN: We are voting on the new 2A.

DR. DAVIS: Just for clarification, we are voting on five through nine.

PARTICIPANT: That is correct.

PARTICIPANT: Question 2A.

DR. NELSON: Five through nine with the assumption epinephrine is available.

MR. JEHN: Okay. We have the vote. We have Dr. Apter as a yes. We have Dr. Davis as a no. We have Dr. Kelso as a no. Dr. Nelson, no. Dr. Riedl, yes. We have Dr. Castells, yes. Dr. Weber is a no. Dr. Saper is a no. Dr. Peterson, yes. And Dr. Lierl, yes. Again, there is five no's and five yeses for modified question 2A with the age groups five through nine.

DR. NELSON: A quick caveat for my no response. Again, it is related to the absence of data and not any

particular signal in this age group. It actually does not indicate the potential for moving forward with this age group of five and up and acquiring data on the fly to support its efficacy.

DR. KELSO: My no vote reflects exactly the same.

DR. SAPER: Likewise.

PARTICIPANT: I agree.

PARTICIPANT: Likewise plus the difficulty with this particular tablet and its dissolution time.

MR. JEHN: Do you have any industry opinion -- okay.

DR. NELSON: I think we are ready for 2B. This is the same question for the age group of 10 to 65, again, with the assumption that injectable epinephrine will be made available at home. We are ready to vote.

MR. JEHN: Okay. We have the vote. It is actually unanimous. Dr. Apter, yes. Dr. Davis, yes. Dr. Kelso, yes. Dr. Nelson, yes. Dr. Riedl, yes. Dr. Castells, yes. Dr. Weber, yes. Dr. Saper, yes. Dr. Peterson. Dr. Lierl, yes.

DR. SLATER: Thank you very much. It is very helpful. With your permission, may I ask you a question, Dr. Saper? Is your concern about the dissolution of the tablet and the esophageal symptoms that an undissolved tablet being swallowed or fragments more likely of

undissolved tablet being swallowed are more likely to cause an inflammatory response in the esophagus?

DR. SAPER: I think that that is a question that has not been answered and those are my concerns. I am not sure whether they are valid or not, but I do not think it has been addressed.

DR. NELSON: Moving onto the next question. No vote involved thankfully. Please discuss whether the available data support the continued efficacy of ORALAIR through one and two years following courses of treatment for the previous three grass pollen seasons. Addressing the question of perhaps disease modification one to two years after treatment. Dr. Kelso.

DR. KELSO: There is some signal I guess in both directions. It appeared that there was some ongoing effectiveness even in the two years off of therapy, but it looked like it might also true that that effectiveness was starting to wane over those two years. I do not think we have enough. I guess it is a signal in both directions. There are some suggestions that it has a persistent effect, but there is also a suggestion that it is wearing off.

DR. WEBER: I certainly agree that it was more robust in the one year after and that the second year looked like the effect was really flagging. It does not look like -- I think it reflects what a lot of the

information on sublingual immunotherapy is that, one, it is not as effective immediately as SKIT and that there is a question about how does these modifying it truly is. I think this just reflects the same kind of result.

DR. LIERL: I would agree with that just looking at the statistics. When you actually looked at the data on the amount that the symptom scores had gone down compared to the baseline, they were staying down in the treatment group and it seemed to be -- it was a good point that may be the placebo patients just got fed up with the study and dropped out, the ones that were more symptomatic. They were like this stuff is not helping me and it has been five years and I am sick of this. The more symptomatic ones did not keep reporting to the study because the placebo patients that stayed in the study were also the ones that were doing better. The difference between the two groups was not that much after five years. But the difference from the baseline to the fifth year and the treatment group was still really good. I do not think we know. I think it was just a weakness of the data collection. I would be interested to see longer term. How long does that improvement and symptoms last? We just do not have the data yet.

DR. CASTELLS: I would agree that in terms of mechanistically we did not have the IgE4 in those years.

We should see if there was a trend with that because that would definitely help us.

The other thing is those patients also were maintained on their medication, their regular medication and we do not really have a pollen count for those years. Whether there were some other additional factors. But again, the mechanistic data would certainly be very important to address that issue.

DR. KELSO: If we compare this to some information that we have about subcutaneous immunotherapy, we know that a year or two does not lead to a persistent effect. If it is three or four or five, we do not exactly know what the magic number is, but we think it is somewhere to three to five years.

And the other difference here is that it is being given seasonally whereas subcutaneous immunotherapy is given year round. It would be very interesting to know if it is still obtainable if there is any way to follow the people who are already in these studies to see what happened on years six, seven, and eight, but also in looking forward to other studies that might be done to specifically investigate and compare three years of therapy, four years, five years worth of therapy. Those would probably be the prime targets and also continue year round therapy versus seasonal therapy in terms of its

durability.

DR. APTER: This would be a good area for post-marketing studies, also mechanistic post-marketing studies, which may not be feasible.

DR. NELSON: That is the perfect segue. Let's go to question four. Please comment on what additional studies if any should be conducted post-licensure.

DR. CASTELLS: I would love to see the data that we had about pregnancy. I think that that would be tremendously helpful to understand what happens with those women. That would be my indication.

I just want to make a quick comment about what we have been talking here about the potential of the reactions occurring mostly in the first and second and third. Again, I am very biased by my background on desensitization. But why not have in one day the 300? You start at 50, 100, and 150. You have the patient in front of you. You see that. For me, it makes a lot of sense in terms of the guidelines that we wanted to reclaim in terms of safety. I am totally concerned about letting a patient go home even with mild asthma, even with an EpiPen and having his second dose at home and being that a Saturday or Sunday. I am not on call 24/7. We would not be able to control what happens to those patients. For me, it makes much more sense to get to the high dose in one day.

DR. DAVIS: I would recommend post-marketing that really we look at these subpopulations so the population of patients that have asthma and really determine whether adverse events and anaphylaxis are higher in those patients.

I would also be interested to know what kind of effect the sublingual immunotherapy has on poly-sensitized patients. Does it affect anything with regard to the dust mite allergy that they have or the cat allergy that they have? And then also for patients who react after meals. Really, we need to impose marketing studies to see what exercise, fever, what happens when people are on their menstrual period. We need to know the factors that would be predisposing to adverse events.

And then finally, I would agree with Dr. Saper and Dr. Lierl that we do not know about eosinophilic esophagitis. Patients that have symptoms suggestive, dysphasia, chest tightness. These patients should be monitored for these signs and symptoms of allergic gastrointestinal disease.

I would want to know also for patients that have systemic reactions. Do they have a positive tryptase just as Dr. Castells said. So really some more data with regard to the systemic effects of grass immunotherapy sublingually.

DR. APTER: You took all the words and more out of my mouth. I certainly second them. You brought up the multi-sensitized patients because most of these patients are multi-sensitized. I think it is important to learn more about whether this has any effect.

DR. KELSO: As far as, I guess, what the FDA would say to the sponsor and I certainly agree with our issues about following more carefully patients in terms of pregnancy, asthma, and potential GI symptoms indicating EOE. But there is another mechanistic question that I guess is not for the FDA to tell the company, but might be of interest which is particularly since part of our concern, if you will, here is that we are just treating people to this one thing that they are allergic to and they are probably allergic to a bunch of stuff. We have some data that patients who are mono-sensitized who go on subcutaneous immunotherapy to that allergen are less likely to acquire new allergies, new sensitizations over time. That would be useful information to know because that might help get around the problem where you are only putting people on this one therapy for this one allergen if we thought that maybe it is preventing them from developing additional sensitizations.

DR. SAPER: Adding to that, in terms of not adding new sensitivities, there is data that with SKIT that

if you start immunotherapy early, you are less likely to develop asthma. And the question is do you afford that same benefit by starting SLIT on a mono-sensitized patient or a patient who does not asthma. Would you be able to afford that same benefit? That would be something worth looking at.

Another suggestion would be there has been a lot of concern here about the up dosing at home that that is really not been how we have been trained as allergists. You can see us all get a little nervous at that. Since there will be a tablet of 100 and a tablet of 200 and a tablet of 300, I am not sure how the packaging is going to work, but thinking of patient factors and our physician unease looking at dosing in the office at 100. Have them take that for a week. We think that the mouth symptoms will likely resolve. Have them come in the next week and dose at 200. Do that for a week. We think the mouth symptoms will resolve. Dose them at 300 and then they are off to go. There may be a lot more comfort within the current allergy community with having some option such as that.

DR. RIEDL: I would just add any data on the elderly. We indicated that in our age indication. But I think as someone who is trained in internal medicine, which is a population that is of course important to treat. We

know they may be less tolerant from a safety standpoint if there are reactions more likely to be on beta blockers and these sorts of things.

It was discussed in question three, but I think the long term or so-called disease-modifying factor is important to consider. As a clinician, if this comes to market, patients making decisions about what treatment, which is an important one I think. If they are going to go to the time and effort and side effects of doing this treatment, is it just good for that season or is there some disease modifying effect? I think that one of the "selling points" of subcu immunotherapy. There is data suggested as disease modifying even after the course has been completed. I personally do not think we have enough data to say much about that at this point.

DR. PETERSON: I am still concerned about children five to ten. I would like to see something done for that population because it certainly is a growing population. They have asthma on top of it, which is growing leaps and bounds.

DR. NELSON: I think that was more with respect to safety or both safety and efficacy.

DR. PETERSON: Probably both. Efficacy. It is something that works. I am concerned about safety. They see results if it is a good product. If it does something,

they will take it. They figure they will grow up. And by 17, they assume they are not going to have it.

DR. DAVIS: This has not been mentioned much, but I would like to see some attention given to especially in the younger population if they have food allergy -- association between the expressions of that food allergy with the administration of the sublingual immunotherapy because it may alter the expression of food allergic disease.

DR. LIERL: In addition to safety studies for patients with persistent asthma, I think efficacy studies for allergic asthma would be great. I know I have patients who have exacerbations every May and June. They are in the ER or in the hospital. They stop doing that when they get their allergy shots built up. I think an efficacy study of the SLIT for the grass pollen would be worth doing.

Also, of course, we have talked about this, but we need more studies on what is the optimal duration of therapy and then what is the duration of improvement post-therapy.

DR. NELSON: Very good. I would only add to also look at potential alternate schedules such as in the second and third seasons. Do we really need four months of pre-treatment going into therapy given a response during the previous season?

Also, something we have not talked about so far is as we offer new products to our patients, one of the reservations is that people do not go on immunotherapy at all because of the difficulty with subcutaneous. What about those who are already on subcutaneous and wish to flip over to a sublingual product. Some prospective work to evaluate how to do those conversations best I think is certainly warranted as well.

DR. CASTELLS: I just wanted to add it is not common. It is just a simple comment about my enthusiasm for the product despite probably it has not been seen with our comments, a discussion to bring the product. And I thank the FDA for bringing the product to the USA and I thank the company too. We have been struggling with those for many years. People do not want to get injections. We have the patients and the clinics saying no if it were a venom we wanted to give to those kids. It might potentially help tremendously those children, maybe take their asthma away or not express the asthma. I think this product could be potentially fantastic and I thank everybody for their efforts.

DR. NELSON: Well stated. Any closing comments from our team from the FDA?

DR. SLATER: No, I think on behalf of all of us I want to thank you all for your very on target and

insightful comments. We are going to take all of this into consideration. I appreciate your votes. We will regroup tomorrow morning.

DR. NELSON: I too and thank you, Dr. Castells, would also like to thank Stallergenes and Dr. Zeldin and their team for outstanding presentations today. Their honesty and open dialogue with us as we get at some of the root issues concerning this important emerging form of therapy in the United States. We will stand at recess until 0830 tomorrow morning where we will review a second product. Have a good night.

(Whereupon, at 4:10 p.m., the meeting adjourned.)